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VOLUME III *August, 1955* NUMBER 8

STUDIES ON CORONARY BLOOD FLOW, WITH EMPHASIS ON THE TREATMENT OF CORONARY INSUFFICIENCY* †

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The beneficial effects of norepinephrine[1] in shock following myocardial infarction have recently been reported (1). Most clinicians regard this drug as one which elevates blood pressure, thus supposedly causing an increase in coronary flow with a beneficial effect on the myocardium.

Experimentally, we have found that norepinephrine is a potent coronary vasodilator and produces an increase in coronary blood flow far in excess of its effect in elevating the blood pressure.

We wish to present the experimental facts which have led us to this conclusion.

MATERIALS AND METHODS

Mongrel dogs, weighing 25 pounds or more, were used throughout the experiments. Anesthesia was induced by Pentothal sodium (5 per cent solution), given to the point of loss of neck reflexes. A cut-down[2] of polyethylene tubing was then inserted into the cephalic vein and attached to a 250-cc. flask of physiologic saline. A very slow drip of saline was given throughout the procedure, in order to keep the cut-down open. Additional Pentothal, 1 cc. at a time, was given as needed through the cut-down.

Intratracheal intubation was carried out by a metal cannula connected with a rubber balloon. This was attached to the Pneophore[3] type of respirator. Pure oxygen was given by the apparatus throughout the procedure.

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* Presented at the Annual Meeting of The American Therapeutic Society, St. Louis, Missouri, November 4–7, 1954.

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[1] Norepinephrine (Levophed) was donated by Winthrop Stearns, Inc., New York.

[2] Inside diameter, 2 mm.

[3] Manufactured by Mine Safety Appliances Company, Philadelphia, Pa.

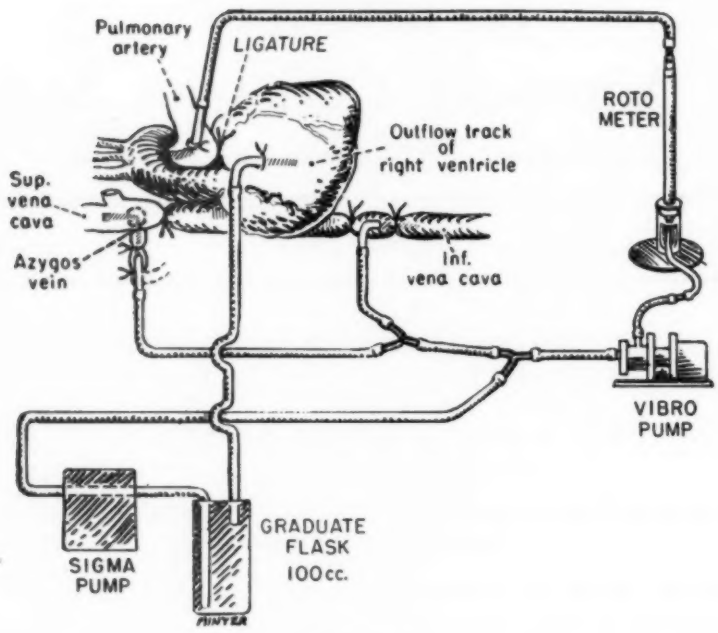

FIGURE 1

Heparin was given in a dosage of 2 mg. per Kg. of body weight and was adequate to keep the blood from coagulating.

Cannulation was carried out as shown in Figure 1. After we had worked this method out independently, we found that Maraist and Glenn (2) had used a similar method for measuring coronary blood flow in 1952. However, our set-up is somewhat simpler. The superior and inferior vena cava are cannulated and a ligature is tied around each cannula so that the entire systemic circulation is shunted around the right heart. The blood is reintroduced into the distal pulmonary artery beyond the ligature. Thus, the entire output of the right heart is from the coronary circulation and should represent the entire coronary venous drainage with the exception of that which is supposed to return to the left heart.

The senior author finds it hard to believe that venous blood can flow into a chamber that has a mean pressure in excess of 90 mm. of Hg. Although it is true that there are certain stages of diastole during which the pressure is very low, the mean pressure is very high, and it would seem that the foramina minima chordae may have more of an arterial than a venous function. Experiments are in progress to test this hypothesis.

Suffice it to say that most of the blood in the venous coronary circulation enters the right heart. The cannula in the proximal portion of the pulmonary artery or the outflow tract of the right ventricle drains into a 100-cc. graduated flask, marked off in 25-cc. portions. The time in seconds necessary to fill 25 cc., divided into 60 seconds and multiplied by 25 cc., gives a coronary flow in cubic centimeters per minute.

The blood from the coronary circulation is re-introduced into the arterial side by a Y-tube on the distal side of the vibropump.

A rotometer[4] is placed distal to the vibropump. When the sigmapump is not running (as happens when the coronary flow is being measured), the reading on the rotometer is that of the entire systemic circulation. Thus, it is possible to compare coronary flow with systemic flow.

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[4] Manufactured by Fisher Porter Company, Hatboro, Pa.

TABLE 1

Flow Studies with Methoxamine Hydrochloride (without Oxygen Measurements)

Date (1954)	Wt. of dog (pounds)	Dose of drug	Blood Pressure (mm. Hg)		Coronary Flow (cc./min.)	
			Before	5 Min. after	Before	5 Min. after
June 6	45	Methoxamine, 3 mg.	40	40	65	52
July 2	30	Methoxamine, 20 mg.	120	100	100	64
July 13	30	Methoxamine, 6 mg.	30	80	136	60
July 13	30	Methoxamine, 10 mg.	24	80	37	64
July 6		Methoxamine, 3 mg.	15	60		224
July 23		Methoxamine, 10 mg.	24	80	37	65
Aug. 6	33	Methoxamine, 5 mg.	85	170	65	166
Aug. 17		Methoxamine, 4 mg.	30	96	65	116
Aug. 23	20	Methoxamine, 2 mg.	40	70	29	29
Aug. 19	34	Methoxamine, 6 mg.	50	85	150	150

Oxygen consumption of the heart in cubic centimeters per minute is calculated by taking the carotid oxygen content (which is assumed to be the same as coronary-artery oxygen content) and subtracting the oxygen content of the blood from the outflow tract of the right ventricle. The difference between the two is the oxygen content per 100 cc. of blood passing through the coronary circulation. This value multiplied by that for the coronary flow in cc. per minute gives the oxygen consumed by the heart in cubic centimeters of oxygen per minute corrected for standard conditions of temperature and pressure.

DISCUSSION

At the beginning of these experiments, many flow studies were performed without oxygen measurements. Table 1 lists the data of 10 experiments in which the effect of methoxamine hydrochloride[5] on blood pressure and coronary blood flow was observed over a period of five minutes. At times, there was a slight decrease in flow, but the findings in general suggest that the effect on coronary blood flow is proportional to the rise in blood pressure.

In contrast, three experiments in which norepinephrine produced an increase in coronary blood flow far in excess of the rise in mean blood pressure are listed in Table 2. It has been our experience that if a small dose of norepinephrine does not produce a rise in blood pressure, a large one will have the desired effect. The experiment conducted on July 22 is an example of this. A first dose of norepinephrine produced a rise in blood pressure from 10 mm. to 30 mm., but doubling the dose sent the pressure to 100 mm.

Natural epinephrine[6] causes a similar increase in coronary blood flow, as noted in the five experiments which are shown in Table 3.

Following administration of both norepinephrine and epinephrine, the increase in coronary circulation was greater than the increase in oxygen utilization by the heart. Table 4 shows the increasing rise of coronary venous oxygen

[5] Methoxamine hydrochloride (Vasoxyl; Burroughs Wellcome & Company, Tuckahoe, N. Y.).

[6] Adrenalin (1–1000 solution), Parke, Davis & Company, Detroit, Michigan.

TABLE 2

Flow Studies with Norepinephrine and Epinephrine (without Oxygen Measurements)

Date (1954)	Wt. of dog (pounds)	Dose of drug	Blood Pressure (mm. Hg)		Coronary Flow (cc./min.)	
			Before	5 Min. after	Before	5 Min. after
July 22	36	Norepinephrine, .5 mg.	10	30	86	125
		Norepinephrine, 1 mg.	30	100	125	700
July 29	32	Norepinephrine, .6 mg.	20	90	250	750
		Epinephrine, 2 cc.- 15 minutes before				
Aug. 2		Norepinephrine, 1 mg.	42	90	25	375

TABLE 3

Flow Studies with Epinephrine (without Oxygen Measurements)

Date (1954)	Wt. of dog (pounds)	Dose of drug	Blood Pressure (mm. Hg)		Coronary Flow (cc./min.)	
			Before	5 Min. after	Before	5 Min. after
July 16		Epinephrine*, .5 cc.	10	70		224
July 23		Epinephrine, .5 cc.	70	60	75	375
Aug. 16		Epinephrine, 1 cc.	20	120	44	750
Aug. 24	31	Epinephrine, .5 cc.		120		1000
Aug. 30	25	Epinephrine, 3 cc.	Less than 40	80		1000

* Adrenalin; 1–1000 solution; Parke, Davis and Co.

TABLE 4

Coronary Flow Studies (with Oxygen Measurements)

Experiment #22 Date—Aug. 10, 1954

B.P. (mm. Hg)	Time	Heart Rate* (per min.)	Conditions of Experiment	Cor. Flow (cc./ min.)	Oxygen Studies					
					On Venous Blood from	O_2 Content (vol. %)	Cor. A-V Diff.**	Capacity	Sat. (%)	O_2 used by Heart† (cc/ min.)
20	11:49	80	Before norepinephrine	72	Carotid	6.7	3.8	8.4	79.7	2.75
					Rt. heart	2.9				
			Norepinephrine, 1 mg. at 11:52							
120	11:53	100		750	Carotid	6.6	1.8	7.7	85.7	13.5
					Rt. heart	4.8				
110	12:05	128	5 min. after 2 mg. Levophed; 13 min. after first dose	750	Carotid	7.1	1.3	7.9	89.8	9.8
					Rt. heart	5.8				

* Counted grossly by observation of the heart through the open chest.

** Oxygen content of carotid artery blood (assumed to be the same as that of the coronary artery blood) subtracted from oxygen content of coronary venous blood taken from right heart.

† Calculated by multiplying A-V difference by coronary flow.

TABLE 5

Coronary Flow Studies (with Oxygen Measurements)

Date--Sept. 14, 1954

B.P. (mm. Hg)	Time	Heart Rate* (per min.)	Conditions of Experiment	Cor. Flow (cc./min.)	Oxygen Studies					
					On Blood from	O_2 Content	Cor. A-V Diff.**	Capacity	O_2 Used by Heart† (cc./min.)	Systemic Flow‡ (cc./min.)
40	2:50	84	No adrenalin	75	Cor. Art.	9.6	6.7	8.7	5	775
					Cor. Vein	2.9				
140	2:59	88	.5 cc. adr. at 2:56	1125	Cor. Art.	9.6	3.4	8.7	38.5	775
					Cor. Vein	6.2				
100	3:07	112	1 cc. adr. at 3:06	625	Cor. Art.	9.9	2.9	9.7	18.8	775
					Cor. Vein	7.0				
90	3:13	140		750	Cor. Art.	9.4	2.8	9.6	21	580
					Cor. Vein	6.6				
40	4:10			750	Cor. Art.	10.1	1.4	10.1	10.5	
					Cor. Vein	8.7				

*, **, † See footnotes to Table 4.

‡ Measured by rotometer.

TABLE 6

Effect of Ligation of Coronary Arteries

Date (1954)	Wt. of dog (pounds)	Conditions	Blood Pressure (mm. Hg)		Coronary Flow (cc./min.)	
			Before	5 Min. after	Before	5 Min. after
June 4	45	Lig. of ant. desc. cor. art.	40	40	52	42
June 16	37	Lig. of ant. desc. cor. art. Methoxamine hydrochl., 20 mg., 20 min. before	54	30	99	68
July 8		Lig. of ant. desc. cor. art.	60	58	116	64
July 13	26	Lig. of ant. desc. cor. art. Methoxamine hydrochl., 6 mg., 20 min. before	80	70	29	22
July 29	32	Lig. of ant. desc. cor. art. Norepinephrine, 0.6 mg., 5 min. before	130	60	500	150

content in blood taken from the right heart. In this experiment, the coronary venous oxygen content rose from 2.9 to 5.8. Thus, the oxygen supply of the heart muscle is raised to such an extent that the heart muscle does not need to take the maximal amount of oxygen out of the coronary blood. Therefore, the coronary venous oxygen content rises.

This was confirmation of the gross observation that after norepinephrine and epinephrine the coronary venous blood turned bright red, whereas after methoxamine it remained black.

The effect of epinephrine on the systemic circulation is shown in Table 5. When the coronary blood flow was increased fifteen times, the systemic blood flow through the rest of the body remained at the same level. The increase in oxygen supply of the heart could be noted from the rise in coronary venous oxygen content.

The effect of ligation of the anterior descending coronary artery on blood pressure and coronary blood flow is shown in Table 6. In the experiment of July 29 the coronary blood flow remained at 150 cc. following norepinephrine, even though the blood pressure fell to 60 mm.

CONCLUSIONS

1. The beneficial effect of norepinephrine in myocardial infarction is due to an increase in coronary blood flow, which is much greater proportionately than the rise in blood pressure.

2. The rise in the oxygen content of coronary venous blood furnishes direct evidence that the oxygen supply of the heart muscle is increased to a greater extent than the oxygen utilization.

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THE SAGA OF LIPOTROPIC THERAPY*

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The word "lipotropic" from the Greek "lipos"—fat—and "tropos"—turning over, or metabolism—may be more historical than accurate as a descriptive term, since the action of the substances known summarily as lipotropic agents may be broader than previously suspected. In this category are four known substances, which have been studied in foods and investigated in animals and man, often with greater enthusiasm than scientific caution; these are: choline, methionine, betaine and inositol. The enthusiasm, more often than not, has been within certain sophisticated boundaries of therapeutic endeavor, namely, attempting to demonstrate that the lipotropic agents either 1) have no effect on metabolism and therefore have no therapeutic value, or 2) if they have an effect, it is better attained through the medium of a diet than by capsules or syrups. If the latter be true, the administration of liver extract and/or vitamin B_{12} should be considered grossly "unsophisticated," and raw liver should return as a medicament for pernicious anemia and allied disorders. This bit of facetiousness is prompted by remarks of several outspoken critics of lipotropic therapy in general.

Choline as a chemical substance was isolated from the bile of pigs in 1849. In 1869 it was established as a component of lecithin. In 1924 (1) it was noticed that depancreatized dogs maintained on sufficient insulin dosage died as a result of fatty infiltration of the liver, but it was found that feeding raw pancreas prevented such an outcome. It was also noted that the activity of raw pancreas was due to its lecithin content. Best (2), in 1932, determined that the action of lecithin in preventing deposition of fat in the liver was due to the choline present in the molecular structure of lecithin.

Inositol, identified as a substance for over a century, but not extensively studied, was first isolated from the urine of a patient with diabetes insipidus in 1858. Both choline and inositol are considered to be components of B complex. Like choline, inositol is part of the phospholipid molecule.

Methionine is an essential amino acid; like choline, it contains a labile methyl group. The detoxifying action attributed to methionine is due to its sulfhydryl group. Methionine is also instrumental in the transmethylation process.

In spite of gaps in our knowledge of fat metabolism, it appears well established that phospholipids play a paramount role in the transport of fat, by incorporation

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Studies on human alcoholic cirrhosis are being conducted at Mississippi State Hospital, Whitfield, Mississippi, with the cooperation of Dr. Carroll L. Busby, Director of Medical Services.

of phospholipid into the interfacial film of the fat particle. The present working concept of prevention of fat deposition in the liver and of removal of already existing deposits, is based on the conversion of neutral fats to phospholipids. Lipotropic substances, administered either in the diet or as a supplement, are essential to this process. The lipotropic activity of a protein diet is due chiefly to its methionine content, which aids choline formation.

The metabolism of betaine and the pharmacodynamics of betaine ingested as a "supplement" are not too well understood; but it appears that this substance does possess, at least under certain circumstances, some lipotropic activity.

ATHEROSCLEROSIS

The time allotted to this presentation prevents even a general discussion of the problems of atherogenesis. The concept introduced a few years ago at the time of the original trial of lipotropes in human atherosclerosis was based on the gross and obviously superficial analogy between fatty infiltration of the liver and deposition of fatty particles in the arterial intima and subintima. Complex though the problem of atherogenesis may be (because of the multiplicity of operating factors), an error in lipotropic metabolism does play a definite role. In a significant percentage of atherosclerotic subjects such an error may be detected by the study of various segments of the broad lipoprotein spectrum. Often (3) the abnormality can be demonstrated in the same individual by more than one technique, *e.g.*, the chemical pattern of serum lipids by extraction methods, or the physical make-up of lipoproteins.

It has been suggested (4) that phospholipid exerts a stabilizing, protective action in lipoprotein metabolism, perhaps through its counter-balancing action on the cholesterol fraction of the lipoprotein molecule. Therefore, another argument for the use of supplementary lipotropes is the fact that both choline—the synthesis of which is aided by methionine—and inositol are incorporated in the phospholipid molecule.

Also in favor of therapeutic and preventive trial with lipotropic substances is the ability of these agents to preserve or even to restore the integrity of the liver. Since the liver is the chief metabolizer of fat and proteins, the disturbance of such metabolism may be corrected by improvement in the liver function. The state of liver function may (as in diabetes mellitus), or may not (as in atherosclerosis) be demonstrated through the performance of chemical tests or morphologic studies.

In several reports (5, 6) we have stressed the statistically significant group correlation between clinically demonstrable atherosclerosis and the level of fasting chylomicrons (lipoprotein particles 0.3 micron in diameter and larger) when determined as a percentage of all particles within the visible segment of the lipoprotein spectrum. In our experience (5) and in that of others (7) administration of a combination of lipotropic agents[1] (in contrast to placebo) resulted in profound lowering of fasting chylomicron levels. These large lipoprotein particles contain chiefly neutral fat and smaller amounts of cholesterol,

[1] Methischol (U. S. Vitamin Corp.), containing choline, methionine, inositol, vitamin B_{12} and liver.

protein fraction and phospholipid. The content of the latter increases with the decrease in lipoprotein particle size. Consequently, a greater serum phospholipid concentration can result in an increased number of particles smaller than chylomicrons, thus tending to lower the level of chylomicrons. This phenomenon has been observed. Since choline and inositol form part of the phospholipid molecule, the administration of these, and perhaps other, substances apparently induces greater phospholipid synthesis. There have been some reports (8) claiming increase of the phospholipid:cholesterol ratio, as determined by chemical extraction techniques.

ALCOHOLIC CIRRHOSIS OF THE LIVER

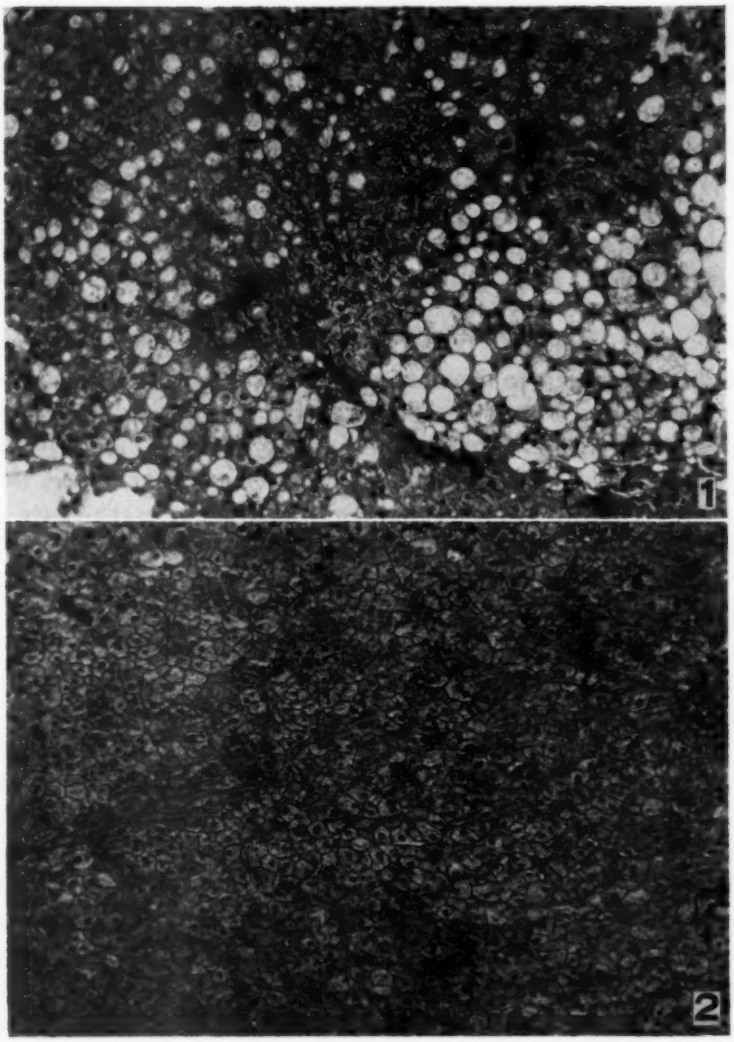
It would be superfluous to discuss here the etiology of fatty infiltration of the liver. It will suffice to state that the causative factors are numerous and that fatty infiltration precedes, causes and accompanies necrosis and fibrosis; in other words, it leads to hepatic cirrhosis. An interesting recent report by Best and associates (9) of Toronto revealed that sucrose administered to rats in amounts equivalent to the caloric content of alcohol sufficient to produce cirrhosis also produced identical hepatic changes. The implication is that alcohol or sugar taken in excess supplants lipotropic-containing foodstuffs and at the same time augments the demand for lipotropic agents by increasing the caloric intake. Thus not only the starvation due to chronic alcoholism but also a badly balanced diet may reproduce Laennec-type cirrhosis, which is most probably a lipotropic deficiency disease.

Our study of human alcoholic cirrhosis was undertaken to determine: 1) the extent to which it is possible to improve the hepatic status of chronic alcoholics with moderate or far advanced cirrhosis, as demonstrated by the results of liver punch-biopsy and/or by liver function tests, and 2) the therapeutic efficacy of the high-protein, high-carbohydrate, high-vitamin diet advocated over a decade ago and now widely used, as compared with the normal hospital diet of 2,300 calories or less containing 50 grams of protein or less (no vitamin supplement), with the addition of lipotropic substances administered orally in large doses and also parenterally if the absorption appears to be impaired.

The answer to the first question is illustrated typically by one of our cases which shows the therapeutic efficacy of lipotropic agents:

J. E., a 42-year-old white male, had been drinking up to one-fifth gallon of whisky per day for about fifteen years. On admission his liver was 8 cm. below the costal margin; liver function tests showed BSP retention, 43 per cent in five minutes, and thymol turbidity, 5.4 Maclagan units; results of a liver punch-biopsy are shown in Figure 1. Because of his clinical status, it was thought advisable to institute intensive oral and parenteral lipotropic (Methischol) therapy. After four weeks of treatment the BSP retention was 26 per cent in five minutes, and thymol turbidity, 0 Maclagan units. An additional three weeks of therapy gave the following results of liver function tests: BSP retention 24 per cent in five minutes, and thymol turbidity, 0.4 Maclagan units. A section from the liver punch-biopsy specimen is shown in Figure 2.

The improvement in other patients now under study can also be demonstrated by changes toward normality in one or more liver function tests.



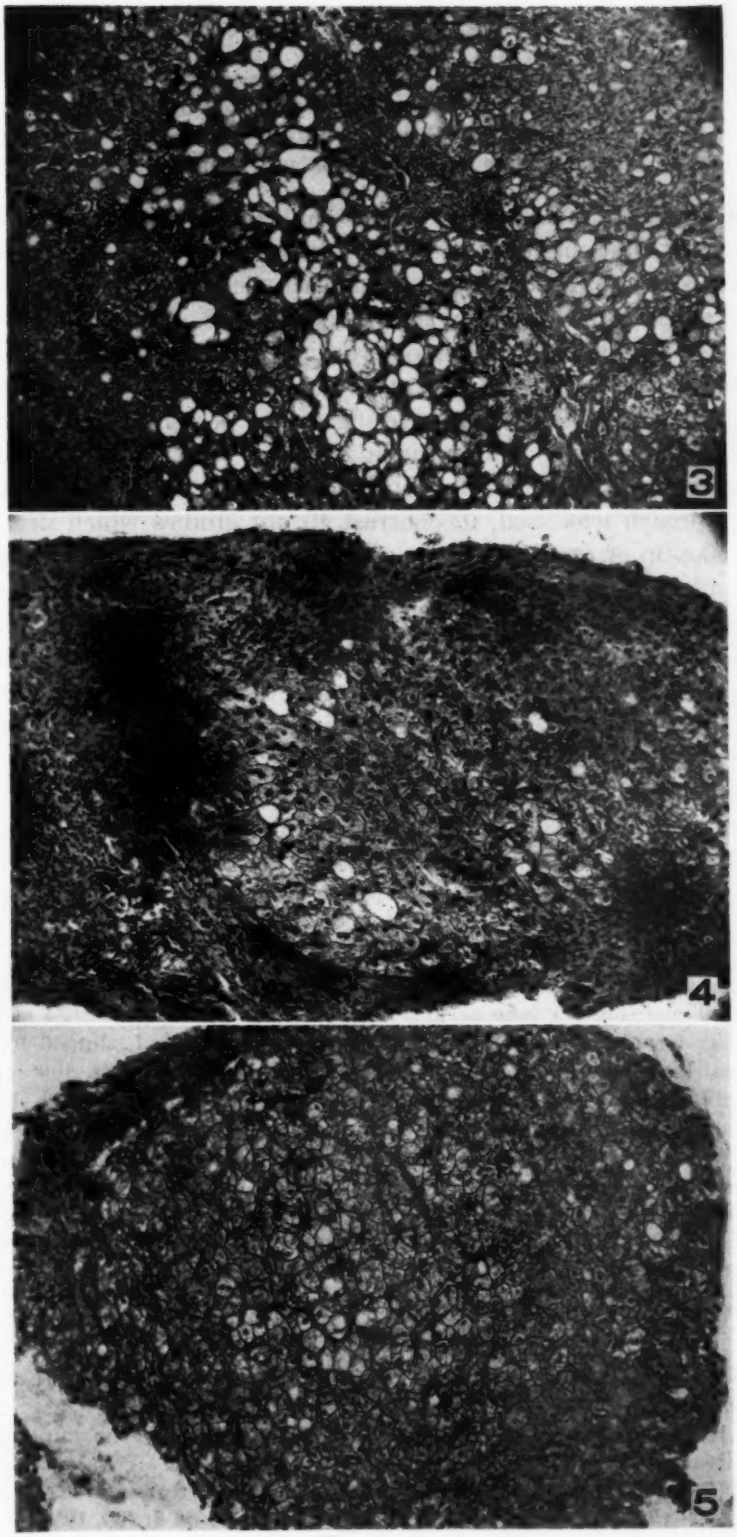
Histologic sections from liver biopsy specimens of Patient J. E.

FIG. 1. On admission.

FIG. 2. After lipotropic therapy.

The following case illustrates the comparison of the relative therapeutic efficacy of the two regimens:

J. B. N., a 44-year-old white male, had been drinking up to one-fifth gallon of whisky per day off and on for twenty-five years. His liver was enlarged 6 cm. below the costal margin and was hard and nodular on palpation. Results of a punch biopsy on admission are shown in Figure 3. BSP retention at that time was 4 per cent in thirty minutes. He was given for four weeks a high-protein diet with cottage cheese and milk *ad libitum*, twelve egg whites daily, high-potency vitamin supplement, and lactose placebo in capsules identical in appearance to those of the lipotropic formula (Methischol). BSP retention was unchanged; results of the biopsy are shown in Figure 4. Then followed a five-week period with the patient receiving a diet of up to 2,300 calories and not more than 50 grams of pro-



Histologic sections from liver biopsy specimens of Patient J. B. N.

FIG. 3. On admission.

FIG. 4. After high-protein diet, vitamin supplement, and placebo capsules.

FIG. 5. After hospital diet and lipotropic therapy.

tein with no other supplements than up to ten capsules daily of Methischol orally and one ampule parenterally. After this regimen, his BSP was 0 per cent in thirty minutes. Results of liver biopsy are shown in Figure 5 (low-power magnification, in order to allay argument that only selected fields were photographed).

The foregoing examples demonstrate that the generally accepted dietary regimen in alcoholic cirrhosis is beneficial, but it is less efficacious from the quantitative standpoint than a regular diet supplemented by lipotropic formula (in this instance Methischol). The fibrotic changes obviously cannot be reversed.

On the basis of our observations, no preventive or curative claims can be made at the present time in the realm of atherosclerosis. However, the effect on lipoprotein metabolism, namely the lowering of the percentage of large particles, is in accord with facts concerning the fate and the effect of lipotropic substances established in previously reported observations. In the latter studies the biochemical approach was used, in contrast to our studies which dealt with the physical make-up of the lipoproteins. Calm and objective scientific appraisal of lipotropic substances has been frustrated by the many extravagant claims. On the other hand, it is not being advanced by the hasty negative conclusions derived from animal experimentation in which so-called arteriosclerosis, or more correctly cholesterolosis, is induced by grossly artificial means; the lesions thus induced differ in both distribution and microscopic morphology from those of the human disease. Such differences also exist in the occasional spontaneous lesions encountered in chickens and swine.

Well controlled studies of human alcoholic cirrhosis have been few, but it is hoped that a fair chance will be given to the therapeutic trial of lipotropic substances in several metabolic disorders which offer promise of true alleviation.

Addendum

A study has been conducted on alcoholic fatty livers in 30 patients who remained under well-controlled regimens for long periods of time. The results, presented at the Annual Meeting of the American Medical Association, Atlantic City, N. J., June 6–10, 1955, demonstrated that both a high-protein diet and a low-calorie, low-protein diet supplemented by moderately large doses of lipotropic substances (Methischol) resulted in diminution of fatty infiltration. In all cases thus studied, lipotropic therapy was followed by complete elimination of fat, whereas a high-protein diet and alcohol withdrawal for up to twenty-four months was followed by marked improvement in, but not complete elimination of, fatty infiltration. One patient lapsed into coma and expired while maintained on a high-protein diet, which confirms the previously advanced theory of occasional poor tolerance for a high-protein regimen.

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LATE RECURRENCES OF PELVIC CANCER, WITH DESCRIPTION OF AN UNUSUAL CASE*

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Some years ago I became interested in the problem of late recurrences of cancer observed well beyond five years following the original treatment. A review of late recurrences in patients seen at the office over a twelve-year span (reported in 1945 (1)) revealed 9 malignant lesions in the pelvis recurring from nine to twenty-six years after apparent cure of the original disease. A five-year arrest of malignant disease is usually considered a "cure" by most physicians and patients, with considerable justification. A recent study (2) of therapy for recurrent carcinoma of the cervix showed that 80 per cent of recurrences occur within the first two years, and that less than 4 per cent are found after five years from completion of therapy for the primary growth. The moral suggested by these studies is that in treating as treacherous a disease as cancer, the five-year "cure" rate should be regarded with great satisfaction, but not with too much assurance. Patients with a five-year arrest should continue with at least annual examinations for the remainder of their lives. This concept needs repeated emphasis. Cancer of the breast and of the thyroid may lie dormant for many years, as occasionally happens with pelvic malignant lesions; but in dealing with cancer, no generalizations are strictly applicable.

Multiple primary malignant tumors have been reported since Billroth (3) described a case in 1869. Since then many instances have been recorded from clinical experience and from postmortem findings, totaling from 1.5 per cent to 7.8 per cent of all patients with malignant lesions (4–6). A new malignant lesion may appear many years after arrest of the first cancer. In many people there seems to be a predisposition or susceptibility to multiple cancers. When many years have elapsed between apparent "cure" of the first malignant condition and the appearance of another cancer in the same or in a contiguous location, the question arises as to whether we are dealing with an unusually delayed recurrence or with multiple primary carcinomas. In cancer of the uterine cervix, a long-delayed recurrence might be attributed to the modifying effects of the cautery or irradiation employed in treatment of the first neoplasm.

A very unusual case illustrates the problem involved.

In March 1924, a widow aged 51 years registered at the Mayo Clinic for relief of metrorrhagia of ten months' duration; she had had pelvic pain for the previous six months, and it had been especially severe for the three weeks prior to admission. Menstrual periods had ceased four years previously. On March 12, 1924, a dilatation and curettage was performed, the curettings showing only hypertrophied endometrium. The cervix looked normal; the uterine body was somewhat enlarged, suggesting a fibromyoma in the fundus.

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A so-called chemical hysterectomy was performed along with the curettage. This consisted of the insertion of gauze soaked with zinc chloride, resulting in destruction of the lining of the uterine canal.

The patient returned in August with recurrences of intermittent pelvic pain; in fact relief of pain by the pelvic operation had lasted only two months. She had returned only to report and would not remain for therapy.

In December 1924, she returned because of vaginal bleeding for the preceding four days. On December 31, 1924, another dilatation and curettage was carried out and ex-

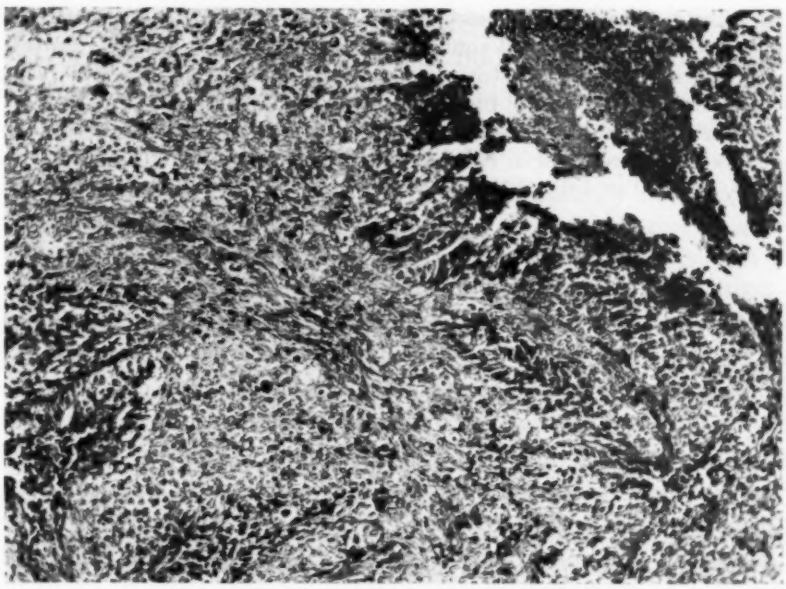

FIG. 1. Biopsy of cervix, 1924

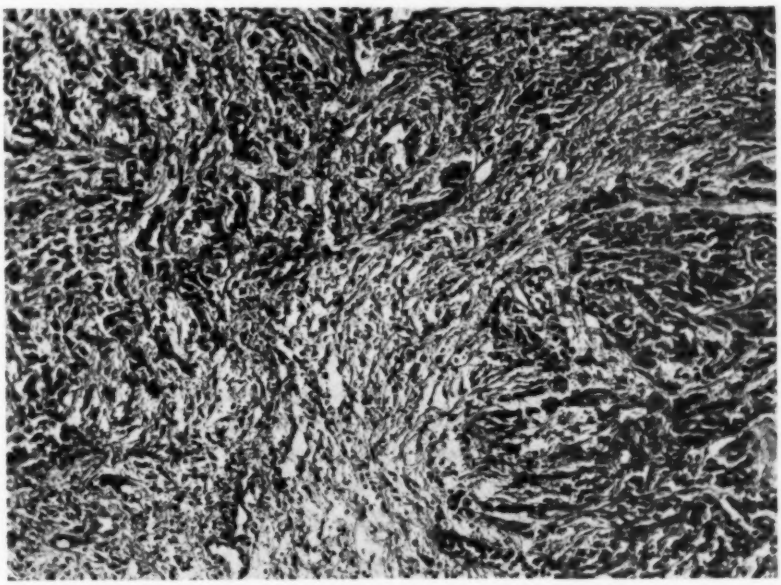

FIG. 2. Biopsy of vaginal wall, 1950

amination of the tissue from the cervical canal showed cancer (Fig. 1). This malignant lesion was judged inoperable by the surgeon, being about stage III in extent. Radium therapy by the intensive divided-dose technic was carried out January 9 through February 6, 1925, with supplementary roentgen therapy following the radium treatments.

Three months later satisfactory healing had occurred and the patient returned for examination at frequent intervals. No evidence of recurrence was noted over the next twenty-five years. In July 1950, an operation was performed consisting of excision of a duodenal diverticulum; careful exploration of abdominal and pelvic structures at the operation revealed no evidence of tumor.

A month later a mass was felt beneath the anterior vaginal wall. August 14, 1950, a biopsy of the vaginal wall showed squamous-cell epithelioma, grade 4, imitating a sarcoma (Fig. 2). Further radium treatment was given August 21 and 22, 1950, using plaques of radium tubes against the area of biopsy.

Three months later enlarged nodes were noted in both groins. High-voltage roentgen therapy was given and repeated in February 1951. However, the patient's downhill course continued and she died in June 1951, at the age of 79 years.

SUMMARY AND CONCLUSIONS

A five-year arrest of a pelvic cancer is so seldom followed by a recurrence in later years that the five-year "cure" yields a rather justifiable sense of security. However, recurrences may become evident many years following surgical or radiologic treatment. The recurrence is usually of the same cell type and microscopic grade. Whether the second malignant lesion is a true recurrence or a second primary cancer in the same or in an adjacent location cannot be decided definitely. The question is rather an academic one, but is of some interest.

In the case report presented, an extensive cancer of the uterine cervix was apparently cured by radium therapy and the patient remained well for a quarter of a century. Then ulceration occurred in the vaginal wall adjoining the site of the original growth and biopsy revealed a grade 4 squamous-cell epithelioma—the same microscopic findings as those reported for the original tumor. This second growth could not be controlled by irradiation and the patient died of cancer ten months later at the advanced age of 79 years.

Study of the microscopic appearance of the two tumors showed distinct differences, although both could be classified as high-grade epitheliomas. The second tumor contained areas resembling adenocarcinoma and other areas imitating a sarcoma. The best guess would appear to be that this represented a second primary cancer following "cure" of the first growth twenty-five years earlier.

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THE CORRELATION OF PHYSICAL AND EMOTIONAL ASPECTS OF DISEASE*

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The patient as a whole is the problem in medicine and should be so considered whenever illness attacks him. He is an acting and thinking being subject to many minor and major physical, emotional and psychic reactions. His normal functional activity and the correlation of its various factors depend on his vegetative and voluntary nervous systems, his endocrine products and various electrolytes. It is affected by stimuli which arise in the viscera, superficial body structures and the cortex. Correlation is such that activity in his physical body may be modified by his thinking and emotions, and his thought and emotions may be affected by stimuli which arise in his physical body. Normal man is so constructed that all action is harmonious, but disharmony may result when disturbances arise in either his physical or his emotional sphere.

In the construction of man's nervous systems there are many ganglia which act as centers for the reception and transmission of impulses from one organ or structure to another. Ganglia in which action between the voluntary and vegetative nervous systems and between the nervous and emotional systems is correlated are situated in the diencephalon. Here are centers which influence many activities, among which are carbohydrate metabolism, respiration, circulation, digestion, body temperature, water balance, dilatation and contraction of the pupil, erection of hairs, secretions of the endocrine glands, and the regulation of the lacrimal, salivary and sweat glands.

Here is located the hypothalamus, in which impulses from the visceral and somatic structures meet and are relayed so as to influence various functions. Impulses from here also are transferred to the cortex, and those which originate in the cortex may be relayed to the viscera and superficial structures. These centers make it possible for man's physical and emotional mechanisms to react as a well balanced, functioning organism in health, and to act inharmoniously in case of disease.

Man in his normal state is under the influence of many emotions of a minor nature—some pleasing, others displeasing—to which he responds promptly. For example, so simple a setting as a beautifully appointed table, food served in an appetizing manner and pleasing company at mealtime all stimulate the appetite and digestion. Disgusting conditions and unfavorable companions, on the other hand, interfere with digestion; but fortunately equilibrium may be quickly restored.

Major emotions, if temporary, may cause only temporary reactions. Cannon (1) showed how fear, hunger, pain and rage by acting through the vegetative

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nervous system throw many body functions out of harmony. For example, a man might see a ferocious wild animal coming toward him. He reacts quickly. His pupils dilate, his circulatory and respiratory mechanisms are speeded up, adrenaline is increased, sugar is forced from the liver into the circulation for muscular use, and his muscles show increased tension. That all energy may be ready for use in fight or flight, digestion and other functions unnecessary for the supreme effort are slowed down or stopped. When the danger has passed, the body functions return to their previous state fairly quickly in individuals who are normally stable, and more slowly in the unstable.

However, if harmful emotions are of a chronic nature, such as those which result from unhappiness, worry, fear, anxiety or persistent pain, then the individual suffers a continuous disturbance to his equilibrium. Both acute and chronic harmful emotions affect the daily lives of many. They are met so frequently in the practice of medicine that it is the duty of the physician to recognize them and to understand their nature, and furthermore to do what he can to alleviate them; for they may interfere seriously with the patient's recovery.

Few illnesses are sufficiently severe to cause the patient to see a physician without some emotional disturbance being present, but the effects are much greater in some diseases and in some patients than in others. Emotional disorders are especially common in chronic diseases in which the patient is continuously cognizant of his illness. He fears that he may not get well or that he may be handicapped and that his future economic, social and domestic relations may be disturbed. This is just as much a part of his illness as the physical disease itself and calls for help. He may have had unbalanced physical and emotional systems previously and they now become increasingly disturbed.

Psychosomatic Medicine

Here is where the old family physician was especially helpful. Patients were his intimate friends. He may have presided at their birth. Often he had been the friend and adviser of the parents and grandparents. Thus patients felt secure in his care. Scientific medicine as we know it today did not exist then; but the patient was known to his physician and was always in the hands of a friend.

Nor was the struggle for existence so demanding a few decades ago. People escaped much of the anxiety and fear caused by the struggles of industrialized life today.

Never before have physicians been able to give better scientific care to their patients, but do we find the patients satisfied with it? Does it not too often lack that personal feeling which carries reassurance and made the family physician of yore so dearly beloved? Scientific medicine alone is too cold for one whose present or future seems threatened because of illness.

This brings us to the recognition of the fact that disease is a psychosomatic problem or, in cases in which the physical problem is of the greater importance, we might call it a somaticopsychic problem. It is important to recognize that the

psychic and somatic are closely bound together, and rarely is one seriously disturbed without the other being also affected.

The example previously mentioned, in which the ferocious animal is in position for attack, may seem far-fetched in case of disease. Nevertheless, we have all observed the reaction of patients suffering from long-standing unhappiness, disappointment, discouragement, fear or pain. These reactions take place over the same nerve paths as the fear of attack. Frequently these emotions, instead of being temporary and quickly subsiding, become chronic. The heart, the respiration, the gastro-intestinal tract and the patient's metabolism may all become chronically disturbed. Treatment of the physical illness, no matter how scientifically carried out, may not be able to relieve the emotional and psychic symptoms. These may be better relieved by a combined physical and psychologic approach, through a physician possessed of human interest and love of mankind.

To emphasize the manner in which emotional and psychic states produce disturbances in the physical man, the term psychosomatic medicine has been devised. Unfortunately this phase of medicine has been neglected by the profession as a whole, and it has been left to those who are particularly interested in the subject of psychiatry to grapple with it. They have described the conditions in psychiatric terms and in so doing have removed it too far from general medicine, where it belongs as much as in psychiatry.

Psychosomatic medicine or somaticopsychic medicine represents a broad conception of the reactions which take place between the psyche and the soma, no matter in which sphere they originate or in which their greatest expression is shown (Alexander (2)). It answers no medical problem for the physician who does not find an organic lesion to say "It is only functional, due to nervousness," or for the psychiatrist to say "The patient is psychically disturbed." This attitude can incapacitate as much as any well recognized disease. Nor does it answer the problem for the psychiatrist to ignore definite medical problems in patients whose trouble seems to be preponderantly emotional or psychic. What the patient desires is relief. Understanding the emotions is as much the duty of the internist as understanding diseases of the heart, lungs, digestive tract or any other system; and understanding physical disease is as important for the psychiatrist as understanding the psychiatric picture.

What a wonderful opportunity in this day when medicine is making such strides in general medicine and psychiatry to bring these phases of medicine together to the glorification of medicine and the benefit of mankind! One can not practice scientific medicine unless he recognizes both phases of the patient's reaction.

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SODIUM METABOLISM; NORMAL AND ABNORMAL*

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PHYSIOLOGY

The early forms of life depended entirely on the fluid environment in which they lived—the sea water. It was an external environment, rather rigidly fixed. The higher forms of life in present times, land-living and air-breathing, depend just as much on a fluid environment; but they carry it within the body. It is an internal environment—the extracellular fluid. If health is to be maintained, this internal environment must remain nearly as constant as sea water itself. Because of its relatively infinitesimal volume compared to the water of the seas, it must be an elastic environment, provided with facilities for adaptation to changes in intake and loss. Moreover, it must be under control of sensitive regulating mechanisms. The lung and the kidney exert a regulating control and are indeed machines of great efficiency, accuracy and sensitivity. Unless damaged or overloaded, they maintain the constancy of the internal environment. MacCallum regarded the establishment of an enclosed aqueous medium as the greatest step forward in the development of the higher forms of animal life and he described the kidney as the most important product of evolution.

I wish to pay tribute to James L. Gamble and his syllabus on the physiology and pathology of the extracellular fluid (1). His analysis is an involved one, but the clarity of his expression has made it possible for physicians to understand the complexities of water and electrolyte imbalance. He visualizes the electrolytes of the extracellular fluid as the chemical framework on which rests the stability of the physical properties of the extracellular fluid. Gamble has shown that water balance depends on the control of the volume of the several fluid compartments.

It is essential that the volume of the vascular compartment be maintained at a fairly constant level; marked variation would inevitably affect the heart and its action adversely. The volume of the intracellular compartment must likewise remain fairly constant; marked variation would have a serious effect on cellular metabolism. There may be an ideal volume of interstitial fluid, but it is evident that extensive changes do not greatly interfere with physiologic processes. The role of the interstitial fluid as an adjustable segment of total body water is understandable.

The interstitial fluid is the pathway between the vascular compartment and the intracellular compartment, by which an interchange of molecules takes place. Its volume variability compensates for the tremendous variations in intake and output of various substances in health and disease.

Osmosis

The movement of water across membranes is in part accomplished by the phenomenon of osmosis, the force or attraction being produced by dissolved

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substance, and the flow of water (solvent) being in the direction of the side of the membrane where concentration is the greatest. The force exerted by a compound is related to the number of molecules in solution. Therefore, a substance in a solution containing the number of grams per liter equivalent to its molecular or atomic weight would have an osmotic pressure equal to that of any other substance in a solution containing the number of grams per liter equivalent to its molecular or atomic weight. (They both have the same number of molecules.)

For example: 23 grams of sodium exerts the same osmotic pressure as 40 grams of calcium. That degree of pressure is spoken of as 1 osmol. Generally, pressures are expressed in milliosmols (1/1000 of an osmol).

The osmotic value of the extracellular fluid is the result of the sum of the pressures exerted by its ionic components.[1] These are determined by the sum of the cations—and sodium is the predominating cation (1).

Concentrations of electrolytes

In expressing concentrations in biologic fluids, the number of milligrams per 100 milliliters is a value which does not permit intelligible comparison. Values expressed as milliequivalents per liter are comparable. One milliequivalent (mEq.) of sodium can replace 1 mEq. of potassium or combine with 1 mEq. of hydrogen.

An equivalent is the gram atomic weight of a univalent element or half of the gram atomic weight of a divalent element. (Calcium—the gram atomic weight is 40; 1 equivalent is 20 grams.) A milliequivalent is 1/1000 of an equivalent. Solutions containing 1 gram molecule per liter contain 1 mole of the substance and they are called molar solutions. One ml. of a molar solution of potassium hydroxide (KOH, 56 grams per liter) or 1 ml. of a molar solution of sodium hydroxide (NaOH, 40 grams per liter) will neutralize 1 ml. of a molar solution of hydrochloric acid (HCl, 37 grams per liter). Milliequivalents per liter may be calculated as follows:

$$\frac{\text{mg./100 ml.} \times 10}{\text{atomic weight}} \times \text{valence}$$

The plasma electrolytes are as follows (approximate average):

Cations	mg./100 ml.	mEq./L	*Anions*	mg./100 ml.	mEq./L
Sodium	326	142	Carbonate	362	27
Potassium	19	5	Chloride	4	103
Calcium	10	5	Phosphate	4	2
Magnesium	1.5	3	Sulphate	1	1
			Organic acid	21	6
Total	356.5	155	Protein	7000	16
			Total	7388	155

[1] Those substances which, when dissolved in water, disassociate into their component elements are called electrolytes. The disassociated elements are called ions. Ions carry electrical changes; those positively charged are called cations and those negatively charged are called anions. For example, a solution of sodium chloride contains Na^+ (cation) and Cl^- (anion).

The sum of the mEq./L for cations is the same as for anions, whereas the sum of mg./100 ml. for cations is far smaller than the sum of mg./100 ml. for anions. Measurement of mass (weight) does not take into consideration the number of molecules in solution, whereas measurement in terms of mEq./L does, and values are accordingly comparable.

Thus, sodium is the major cation and chloride the major anion. The concentration of both is regulated by the kidney. The anion HCO_3— (bicarbonate) is the most easily adjustable. An increase in other ions robs the bicarbonate ion of base. The bicarbonate ion is released as carbonic acid, which is under control of the respiratory mechanism. A decrease of other anions releases base and there is a corresponding increase in bicarbonate ions derived from carbonic acid held in the plasma.

By this mechanism, disastrous changes in reaction of plasma are avoided; the uncovering of base is prevented and, conversely, base is available for covering an increase in acid radicals.

Function of sodium

From the foregoing it is evident that, as the major cation, sodium largely controls the osmotic value of the extracellular fluid and further, as the major cation, it plays an important role in acid-base balance in both the bicarbonate and phosphate systems.

Normal values for sodium

The average adult body contains about 65 grams of sodium. Intracellular sodium has been estimated to be 6 grams. Of the total, 21 per cent is combined with calcium of the bones and 15 per cent is contained in the plasma.

The normal serum sodium concentration is 137–142 mEq. per liter (315–338 mg./100 ml.).

The daily intake in health is estimated at 3–10 grams as sodium (8–15 grams as NaCl). About 4–12 grams (as NaCl) are lost in the urine, feces and sweat each day. The daily requirement has been estimated to be 4–15 grams as sodium chloride.

FACTORS IN THE CONTROL OF SODIUM METABOLISM

The kidney

The glomerular filtrate is essentially plasma water and dissolved substance minus the protein. In the tubule, glucose, electrolytes and water are reabsorbed. About seven eighths of the filtered sodium is subject to obligatory reabsorption in the proximal tubule and the remainder to facultative reabsorption in the distal tube, under the control of the hypothalamus and posterior pituitary gland (4). When the posterior pituitary hormone is secreted or administered, reabsorption of water increases and the urine becomes hypertonic; relatively more water than salt is reabsorbed. A fall in osmotic pressure exerted by the blood in the internal carotid artery will cause inhibition of secretions of the posterior pituitary hormone. The distal tubule will now absorb more salt than water.

The adrenal cortex

The adrenocortical hormones (mineralo-corticoids) cause salt retention by the passage of sodium through the renal tubule cells. Failure of adrenocortical hormones (Addison's disease) lowers tubular reabsorption of sodium and permits salt loss.

SODIUM DEPLETION

Sodium depletion requires:

1. Abnormal losses of sodium and chloride.
2. Adequate intake of water.

Loss of fluid by vomiting, sweating, or by polyuria may encourage the over-enthusiastic administration of water or salt-free fluids, without regard for the electrolyte loss.

There is an inevitable loss of some sodium in the urinary excretion. The result is a fall in extracellular fluid as the kidney excretes water in an effort to maintain the correct electrolyte concentration in the vascular and the interstitial compartments.

Blood pressure falls, and there is peripheral circulatory collapse with a rising concentration of urea in the blood.

In addition to loss through gastro-intestinal secretions, sweat and urine, a severe loss of fluid and electrolytes may occur from wound surfaces. Functional loss may occur from local accumulations in the serous cavities; burns and extensive trauma may cause accumulation inside of body. Hemorrhage, external or internal, results in fluid and electrolyte depletion.

In some cases of renal insufficiency with marked tubular damage, there may be a failure to reabsorb salt. The kidneys, under these circumstances, do not respond to endocrine therapy.

As salt depletion progresses, less salt is excreted by the kidney, but water excretion continues in an attempt to maintain ionic equilibrium. Plasma and interstitial-fluid volumes decrease. Peripheral circulatory collapse, a rising blood urea level, and hemoconcentration characterize severe losses. Death results from loss of osmotic pressure of the extracellular fluid.

SODIUM RETENTION

Sodium retention in combination with water retention occurs as the result of diminished glomerular filtration, and during administration of mineralo-corticoids. A high serum sodium level is seldom seen clinically even when sodium retention exists.

Diminished glomerular filtration may result from decreased cardiac output. The retention of sodium is accompanied by retention of water, in order to maintain ionic equilibrium. The volumes of interstitial fluid and vascular fluid are increased. The increase in vascular fluid adds to the work of the heart. Thus there is a vicious cycle—as sodium retention rises, cellular dehydration follows; potassium passes out of the cells of the heart muscle and sodium replaces potassium. Sodium inhibits the enzyme system in the heart which converts energy-rich pyruvate to phosphocreatine. In this manner, cardiac activity is depressed.

Sodium retention leads to cellular dehydration in the presence of an increased volume of interstitial fluid and edema.

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A NEWER METHOD OF NICOTINIC ACID THERAPY IN HEADACHE OF THE VASOCONSTRICTIVE TYPE*

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In a preliminary report read before the American Therapeutic Society in Chicago in June 1952, I reported 5 patients with vasoconstriction headache, who were improved or well. The use of nicotinic acid therapy for the treatment of some types of headaches was suggested by the fact that nicotinic acid relieved post-spinal cephalgia and various depression states.

Fifty cases are presented in this paper, and descriptive details are listed in Table 1. These patients are of particular interest because all of them had previous treatment for their headaches without relief. Forty-five received ergotamine tartrate at one time or another, with unsatisfactory results; in fact, in a few instances the headache was intensified following the use of this drug. It is important to emphasize that in nearly every instance the patient presented some form of depression state. The results obtained following nicotinic acid therapy were very satisfactory in 44 of the 50 cases.

It is of interest to note, in a perusal of the literature, that there are many reports of relief of the migraine syndrome in emotionally unstable individuals following nicotinic acid therapy. Crosby (1) pointed out good results with the use of nicotinic alcohol (Roniacol tartrate), which is slowly converted into nicotinic acid in the body. Loman, Rinkel and Myerson (2) showed that nicotinic acid, in some unknown manner, causes an increase in brain volume, and it is exactly this action which is desired in the treatment of post-spinal and post-pneumoencephalographic headache.

Moore (3) had demonstrated a rise in cerebrospinal fluid pressure in 2 patients and dilatation of the pial blood vessels in cats following the administration of nicotinic acid, but Loman, Rinkel and Myerson were unable to find any change in the cerebrospinal fluid pressure, cerebral arterio-venous oxygen difference, or the size of retinal blood vessels following the injection of large doses of monoethanol amine nicotinate. Friedman (4) and his associates pointed out that in approximately 25 per cent of migraine patients and in 55 per cent of tension patients the headaches were improved to some extent by administering a placebo but, in general, this type of treatment is ineffective.

The tension type of headache is usually caused by changes in the size of the cranial vessels as well as by an increase in tonicity or spasm of the skeletal muscles of the neck and head, since both vascular and muscular influences seem to be present. Peters (5) asserts that between the typical tension headache and the typical migraine headache there are all degrees and combinations. The patient

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TABLE 1

*Differential Diagnosis of Migraine and Tension Headaches**

	Migraine	*Tension Headache*
Age of patient at onset	Begins before age of 20	Begins in early decade of life
Sex of patient	Female, 60%	Female, 70%
Familial history	Present in 65%	Present in 40%
Frequency	Daily headaches infrequent	Often more or less constant, with exacerbations
Prodromata	Present in 75%	Rarely, if ever, present
Type of pain	Throbbing	Dull, constrictive, or throbbing
Location of pain	Unilateral; often supraorbital	Bilateral; often begins in occipital region
Effect of ergotamine	Relief (usually)	No relief; often made worse
Followed by depression	Lassitude, but not depression	Usually followed by depression
Duration of headache	Often a few hours; rarely more than three days	Often lasts for several weeks, with few periods free from discomfort
Patient aware of cause of pain	Rarely	Usually
Associated symptoms	Visual and gastro-intest. irregularities; disturbances of psyche and autonomic nervous system (more severe)	Anxiety, depression, nausea, photophobia (less severe)
Condition during headache	Patient is ill and in marked distress; unable to work	Patient not very ill; able to work most of the time.

* Part of this table was taken from an article by Friedman and Von Storck (4).

will often remark "I have two kinds of headache" and will describe 1) the dull, constant bilateral more or less daily type, and 2) the usually unilateral, throbbing type, associated with ocular and gastro-intestinal symptoms, which occurs once or twice each month.

It has been pointed out that migraine patients are very prone to show severe emotional states which are provoked by a clearly defined condition. Wolfe (6) and many others have called attention to this fact, and have noted that such periods are associated with an increase in the intensity and frequency of the attacks. Pfeiffer (7) finds there are no consistent changes in the levels of blood electrolytes during relaxation or migraine headache, but that the attack is accompanied by a relative hemoconcentration. There are many other known factors which can be correlated with changes in blood volume and peripheral vascular tone.

More recently Friedman and Von Storck and others have attempted to distinguish between the ordinary migraine headache and the so-called tension headache. Their views are in accord with ours, based on results obtained with the forms of therapy suggested. They believe that tension headaches occur in direct relation to constant or periodic emotional conflicts of which such patients are usually only partially aware. These emotional states may provoke a headache by producing changes in the caliber of the cranial vessels and concomitant spasm of the skeletal muscles of the head and neck.

CRITERIA FOR THE USE OF NICOTINIC ACID

In the treatment of tension headache, it is important to be guided by certain factors. In order to obtain satisfactory results from the use of nicotinic acid therapy, we have postulated four criteria for differentiating tension headache from migraine. These criteria are as follows: 1) there is no aura, 2) the patient knows what causes the headache, 3) the headache is followed by some degree of depression, and 4) the patient is not relieved or is made worse following the administration of ergotamine or dihydroergotamine.

1. *Aura*

There is usually a striking absence of prodromata or pre-headache symptoms. Of our 50 cases of tension headache, in only 2 instances did prodromal symptoms occur. The patient is often awakened with the headache, which is described as a dull, throbbing or constrictive. The headache is ordinarily bilateral and often lasts for several hours or even days. In fact, upon close questioning, the patient will describe it in many instances as more or less constant but with exacerbation of a more severe pain at intervals.

On the other hand, in migraine headache, prodromata occur in about 75 per cent of the cases, manifested by such signs as scotoma, gastro-intestinal upsets, or disturbances of the autonomic nervous system. The pain is usually unilateral occurring frequently in the supraorbital region, and often described as throbbing. The patient is actually ill, seeks a dark room, wishes to be alone, and is unable to carry on his normal duties. After a variable period of time the pain disappears, and in the interval between the attacks the patient is entirely normal.

2. *Cause of headache*

In the vast majority of cases the patient seems to know the cause of his headache. The factors producing the headache in our 50 cases were as follows: diet in 1 case, excitement in 10, overwork in 17, premenstrual tension in 7, occupational tension in 1, worry in 1, dislike of employer in 1, Ménière's disease in 5, mother-in-law trouble in 1, and unknown cause in 6 cases. Emotional factors are usually easily found. These may be constant (in which case the headache is usually constant) but are more often intermittent (then the headache is intermittent).

The headache may be due to living conditions, as in the case of one woman who was afflicted only when entertaining some unwelcome guest. Working conditions may be the cause; for instance, a patient may dislike his occupation or a fellow worker, or may resent being asked to work overtime by an employer toward whom he entertains a feeling of hostility.

3. *Depression*

Depression symptoms are the most commonly noted. They occurred in 34 of our 45 cases. It is remarkable how often the patient will volunteer the information that the attack is followed by a sense of depression which may last from one hour to several hours.

The migraine sufferer on the other hand is often tired but usually does not feel depressed.

4. *Effect of ergotamine*

I have had no success with nicotinic acid in those cases which are relieved by ergotamine tartrate (Gynergen). This is another reason for believing that tension headache is due to a vasoconstriction of the vessels. None of our cases was helped by ergotamine therapy. In 4 instances the headache was made worse.

During the past year, nicotinic acid was not used unless the patient fulfilled at least three of the four criteria postulated.

Many authors are of the opinion that nicotinic acid is indicated in various depressed states. Notably, Sydenstricker and Cleckley (8) believe that factors other than dietary disturbances play an important role in vitamin deficiency and that some unknown factor may also influence the failure of the neurones to receive and utilize an adequate supply of vitamins. According to Cleckley (9), it is probable in some cases that the beneficial effect observed is the result of vasodilatation rather than the correction of a deficiency state. Aring (10) concludes that there is an increase in the cerebral blood flow following the use of nicotinic acid. Goldzieher and Popkin (11) recommend its use in the treatment of severe ecliopathic migraine. Crosby suggests the use of nicotinic alcohol (Roniacol tartrate) in the treatment of post-pneumoencephalographic headache and reports good results in a few cases: his recommendation is based on the good vasodilating action of this drug in the extremities. With these views in mind, it seems justifiable to use nicotinic acid in those cases not helped by ergotamine, since it is believed that in tension headache the pain is caused by vasoconstriction of the cerebral arteries rather than by dilatation of the extracerebral arteries.

Although the use of nicotinic acid is not new, the oral route of administration and insufficient dosage led to poor results and thus to its discontinuance in the treatment of headache. Washburne (12) published encouraging results with this drug in certain depressed states. The general outline of treatment which he recommended was followed in our cases of tension headache. In addition, we utilized the combined intravenous and oral routes, and administered a larger dosage of nicotinic acid.

In an exhaustive search of the literature, no contraindications to the use of nicotinic acid could be found.

RESULTS

The relief afforded following nicotinic acid therapy is always in proportion to the intensity of the vasomotor reaction, which is characterized by bright red flushing of the face, spreading rapidly over the entire trunk and often accompanied by tingling of the fingers, and lower extremities and with a marked sensation of heat. However, this reaction usually subsides in about ten to fifteen minutes, and there has never been any complaint if it was explained to the patient before the treatment was begun. Often, if the patient sits up too

soon, there is a sensation of dizziness due possibly to postural hypotension; this can always be obviated by placing the patient in a prone position and having him remain in the bed until the flush has subsided.

As nicotinic acid sometimes causes constriction of the splanchnic vessels, it was noted in a few instances that the patient complained of severe abdominal pain, which was quickly relieved by giving some form of atropine, or by hypodermic administration of methylamino-methylheptene (Octin) in 1-cc. dosage. Although there is the possibility of this rare side-effect, it does not lessen the effectiveness of the drug in relieving the headache, probably because it usually occurs late.

After frequent injections, occasionally it is impossible to get into the vein. If this occurs, the drug is given intramuscularly, using 200 mg. (100 mg. in each arm). This method causes a great deal of local pain, and the results are not as good. The pain can often be relieved by the application of an ice cube, wrapped in a small towel, applied to the site of the injection.

One of the best recommendations for the use of nicotinic acid orally and hypodermically (sterile technic) is that it is a perfectly safe procedure, and there are no contraindications, regardless of the age or physical condition of the patient. No patient has ever refused to take the treatment; they usually come in and ask for it.

In cases of premenstrual headache in which the usual drugs are of no avail, nicotinic acid therapy offers excellent results and should be given about twenty-four hours before the onset of headache. After a few periods of intravenous medication, oral administration is usually all that is necessary, provided the patient takes the drug orally for about six to eight months.

This type of treatment has also been used in persons with a tendency to Ménière's disease associated with endolymphatic hydrops. It seems to give as much relief as the use of histamine and is much less hazardous. Williams (13) recommends its use, and Porter (14) of Baltimore is very enthusiastic about it.

METHOD OF ADMINISTRATION

Intravenous administration: It is important to emphasize that the treatment should begin with nicotinic acid administered by the intravenous route. In all instances this should be immediately followed by oral administration. A solution of nicotinic acid (100 mg. in 10 cc. of sterile water) is injected intravenously, usually at the rate of 20 to 30 drops per minute. The rapidity of injection is determined in each case by the degree of flushing and warmth which ensues. The time required is usually about ten minutes. The intravenous therapy is continued as follows: for a two-week period, three times a week; for another two-week period, twice a week; for another two-week period, once a week; then once every other week for two doses, once every three weeks for two doses, once every four weeks for two doses, once every six weeks for two doses, and once every two months thereafter when necessary. At the conclusion of the first treatment, when the patient leaves the office, a prescription is given for two hundred 50-mg. tablets of nicotinic acid together with a typed schedule of instructions for its oral use; the first oral dose is to be taken preceding the next meal.

Oral administration: The schedule of oral administration is as follows: (a) For the first two days, three 50-mg. tablets are to be taken at 15-minute intervals preceding each meal. Example—if breakfast hour is 8:00 a.m., the first tablet is taken at 7:15, the second at

7:30, and the third at 7:45 a.m. (b) If no headache or nausea occurs, the dosage is increased on the third and fourth days as follows: four 50-mg. tablets are taken before each meal, according to the 15-minute schedule, the extra tablet being added to the first dosage. Example: 100 mg.—50 mg.—50 mg. (c) On the fifth and sixth days, five 50-mg. tablets are to be taken before each meal, the extra tablets being added to the first and second dosages. Example: 100 mg.—100 mg.—50 mg. (d) On the seventh and eighth days, six 50-mg. tablets are to be taken according to the 15-minute schedule before each meal, two tablets being taken together. Example: 100 mg.—100 mg.—100 mg. Thus, by the eighth day, the total daily dosage is 900 mg., and additional amounts may be given if necessary. The patient is maintained on the maximum dosage for a period of from seven to ten days, at the end of which time the dosage is decreased at the same rate at which it was increased. The average period for administration of nicotinic acid thus varies from two to six weeks, after which most patients are given 100 mg. three times a day, depending upon their reaction and condition.

As has been previously stated, the rapidity of the initial relief following the use of nicotinic acid is always in proportion to the intensity of the vasomotor reaction. After the second or third injection, side reactions if they occur, gradually become less severe. It must be emphasized again that the drug should be given slowly at first, but fast enough to get a definite flush.

DISCUSSION

Experimental and clinical observations point to a better understanding of the fundamental differences between migraine and tension headaches.

Giffin (15) asserted that tension states seem to be related to current situations, whereas migraine seems to be related to early psychogenetic factors. In tension headache patients have a feeling of insecurity, which leads to a sense of hostility to themselves and others with whom they associate and work. A sense of frustration often limits the individual in adjusting to his surroundings and manifests itself in a desire for affection and love.

The migraine individual on the other hand is not able to adjust to surroundings, whether the reaction be emotional, metabolic or allergic. Migraine headache has certain specific characteristics, whereas tension headache shows less of a set pattern.

Nicotinic acid therapy should be used only when there is a long-standing, more or less constant headache, usually not preceded by an aura, and followed by a sense of depression. The method of administration is of considerable importance and is commensurate with the good results obtained.

SUMMARY

Fifty cases of tension (vasoconstriction) headache are presented.

Four criteria for differentiating between migraine and tension headache are outlined.

Migraine is best treated with ergotamine, whereas tension headache is best treated with nicotinic acid.

For successful nicotinic acid therapy of vasoconstriction headache, the method of administration (intravenous plus oral) is highly important.

The favorable results obtained in this form of long-standing headache would appear to be due to the vasodilating effect of nicotinic acid.

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THE USE OF THE RIGHT COLON AS A SUBSTITUTE GASTRIC POUCH AFTER TOTAL GASTRECTOMY*

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Since the introduction of total gastrectomy for the treatment of gastric carcinoma, physicians have been confronted with the unpleasant fact that the cure in some instances may impose greater disability than the disease (1, 2). Postoperative morbidity has varied in intensity from minimal vague epigastric fullness to progressive and inexorable inanition, cachexia, and even death (1). Impairment of digestive function, anemia, malnutrition, stricture at the anastomosis, steatorrhea, diarrhea, and the so-called "dumping syndrome" are all encountered (1–4). However, careful study of these complications reveals that only the anemia is actually due to a nutritional defect directly imposed by total gastrectomy (1), and this can usually be remedied by oral hydrochloric acid, absorbable ferrous iron, vitamin B_{12}, and the like (1, 4). The other sequelae, such as malnutrition, steatorrhea and diarrhea, are largely due to excessively rapid food passage through the jejunum, and therefore represent a mechanical rather than a biochemical problem (1).

Numerous attempts have, therefore, been made to replace the missing stomach by surgical reconstruction (1, 2, 5).

HISTORICAL REVIEW

Conner (6), in 1884, attempted the first total gastrectomy on record and Schlatter (7), in 1897, performed the first successful total gastrectomy. In both cases, continuity was restored by anastomosing the end of the esophagus to the side of a loop of jejunum. This technique, with modification, has remained the procedure of choice even though its limitations have been well documented. The second type of reconstruction consisted of an anastomosis between the esophagus and duodenum. This procedure has had, of necessity, a limited application, since it is technically impossible in a fair number of cases. Horsley (8), in 1935, modified the esophago-jejunostomy by implanting the duodenum into the side of the efferent loop of jejunum. Roscoe Graham (9), in 1940, added an entero-enterostomy plus a telescopic type of esophago-jejunostomy with considerable improvement in postoperative function and a decrease in the irritating regurgitative esophagitis. Engel (10), in May 1944, extended the entero-enterostomy completely around the anastomotic loop, thus creating a pouch with afferent and efferent loops entering and emerging from the inferior portion. Longmire, in November 1944, using this technique, reported ischemic necrosis at the apex

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of the jejunal loop with a subsequent fatal peritonitis. Hunnicutt (5), in 1949, initiated the use of the terminal ileum and right colon as a gastric reservoir and in 1953 reported 17 such cases, with 7 operative deaths. Lee (1), in 1951, after preliminary work on dogs, used the Hunnicutt procedure in 3 patients, with satisfactory early results. Hunt (11), in 1951, modified the Roux-en-Y (12) by anastomosing the end of the jejunum back onto itself to create a pouch before uniting it to the end of the esophagus. State, Barclay and Kelly (13), in 1951, reported a case with a transposed segment of transverse colon inserted in an antiperistaltic fashion between the esophagus and the duodenum. The immediate result was encouraging. In 1952, Longmire *et al.* (2) reviewed his experience with the aforementioned procedures and added to these the use of a transposed jejunal segment brought through the transverse mesocolon and inserted into the gastric bed in an isoperistaltic fashion. He used this method in 12 cases, with 1 operative mortality. He concluded that the function apparently equalled that of the colon segment, with less attendant operative hazard.

The Hunnicutt technique (5) involves isolating the distal ileum and right colon, and interposing this isolated segment between the esophagus and duodenum. Lower intestinal continuity is restored by an anastomosis between the proximal ileum and the distal transverse colon (1). The following case report summarizes the clinical course with laboratory observations in a patient who underwent this operation.

CASE REPORT

Mr. J. M., a 69-year-old white male, was first seen on June 19, 1953, complaining of constipation, a 15-pound weight loss with anorexia of two months' duration, and a single bout of nausea and vomiting.

Physical examination showed a well developed white male in no acute distress, manifesting some evidence of recent weight loss. His skin was pale and somewhat inelastic, and he weighed 186 pounds. With the exception of a minimally emphysematous chest and lungs, findings on physical examination, including proctosigmoidoscopy, were within normal limits.

Initial laboratory studies: hemoglobin 9.5 Gm./100 ml., hematocrit 31 per cent, sedimentation rate 26/hour (corrected), and total serum protein level 6.0 Gm. per cent. Results of urinalysis, and determinations of the white blood count, blood urea nitrogen, and serum chlorides were within normal limits. Stools had a strongly positive (+4) reaction for occult blood. A barium enema showed nothing remarkable. An upper gastrointestinal x-ray series revealed a large, ulcerated carcinoma arising from the lesser curvature, and apparently extending from the antrum to a point near the cardia.

On July 3, 1953, laparotomy was performed and a massive carcinoma was found, which involved the antrum and pars media, and extended along the lesser and greater curvatures to the re-entrant angle of the stomach. There were nodes along the left gastric vessels, extending down to the celiac axis. The liver was free of metastasis, so total gastrectomy and omentectomy were carried out. Microscopy later confirmed an undifferentiated carcinoma (Borman's Class IV). Utilizing the terminal ileum and ascending colon in the manner described, a substitute gastric reservoir was fashioned.

The patient had a very smooth postoperative course without nausea or abdominal distention. He tolerated all liquids well from the second day. Regular bowel movements were noted after the third postoperative day. An upper gastro-intestinal series was carried out on the eleventh day, revealing good filling of the new stomach but a marked delay

in emptying. The patient was discharged on the twelfth postoperative day, weighing 166 pounds. His hemoglobin, initially 9.5 Gm., was 11.3 Gm./100 ml. at the time of discharge. On August 13, 1953, six weeks postoperatively, an upper gastro-intestinal x-ray series demonstrated a normally functioning stomach, except for slightly accelerated emptying. At five hours, the head of the barium meal was in the transverse colon.

For nine months the patient enjoyed a comfortable recuperation. He ate three regular meals daily, which included red meat, vegetables, fowl, eggs, cereal and fruits. Between September 1953 and December 1953 he visited in Ireland. During this time he experienced one episode of severe, persistent diarrhea, which promptly subsided upon his return to the United States. His bowel habit was otherwise regular. Results of an oral glucose tolerance test, performed in December 1953, were entirely normal. There was no evidence of increased fat in the stools. As late as May 1954, tests showed liver function to be satisfactory (with the exception of slight BSP retention).

His medication included a mild sedative antispasmodic, a hematinic capsule, and weekly vitamin B_{12} injections. He resumed his normal intake of several glasses of beer daily plus a "shot or two."

In April 1954, the patient began to experience abdominal pain following the ingestion of his evening meal. From this moment, he suffered increasing distress, accompanied by failing appetite, weight loss, nausea, and postprandial cramping. An upper gastro-intestinal x-ray series, completed in May 1954, again demonstrated satisfactory filling of the pouch, with normal emptying.

By early June 1954, his liver was definitely palpable, although not nodular. He was hospitalized for supportive therapy during this month, and again on July 23. He died on August 1, 1954, thirteen months after operation, due to widespread metastases, inanition, cachexia, toxemia and obstructive jaundice. Permission for autopsy was denied.

COMMENT

This patient underwent total gastrectomy for carcinoma with subsequent reconstruction of a substitute gastric reservoir from his ascending colon and terminal ileum. From the functional standpoint, his pouch performed efficiently in accommodating three regular meals daily, and emptying occurred in a manner roughly anticipated of the normal stomach. The resultant diminished rate of intestinal flow permitted adequate fat absorption and a comfortable, normal bowel habit. Absorptive mechanisms were otherwise satisfactory, as reflected by a normal oral glucose tolerance curve, progressive weight gain, and the maintenance of normal serum protein levels. The patient's freedom from unpleasant subjective symptoms and tolerance of relatively energetic social pursuits for a period of nine months were particularly gratifying.

CONCLUSIONS

We do not mean to imply that total gastrectomy with the surgical production of an artificial gastric pouch is the operation of choice for gastric carcinoma, nor can it be expected to improve the survival rate. However, until there is universally early diagnosis (the crux of the gastric-carcinoma problem) and until adequate chemotherapy and/or other effective methods of treatment become realities, the performance of total resections will continue, particularly when lesions arise near the cardia. Since this operation gives rise to distressing sequelae, the added risks of a "substitute stomach" seem justified. At least the mechanical

efficiency and physiologic performance of such substitute reservoirs deserve more careful study in the future.

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EVALUATION OF ORALLY ADMINISTERED PENICILLIN*

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Other considerations being equal, if one is given the choice of administering a medication orally or parenterally, it is preferable to administer it by mouth. There has been reluctance to accept this statement with regard to penicillin, but there is currently an unmistakable trend toward oral penicillin therapy. In Sweden at the present time 50 per cent of the penicillin used is administered orally (1), and in this particular the Scandinavians are in advance of the United States in the acceptance of this route of administration.

The original penicillin team at Oxford recorded (2) the first successful use of orally administered penicillin, in the treatment of a staphylococcal urinary-tract infection (their Case 6). Why, then, has it taken so long to accept this route of administration? In 1941 a milligram of penicillin had a potency of only 40 to 50 units, as compared to today's 1,670 units. Florey and his associates were compelled by practical considerations to recommend only parenteral administration of the then new and rare antibiotic. The first American investigators made the same recommendations (3), and it is only within the past few years that these authoritative pronouncements of yesterday have been modified by new data. Many of the original investigations have been repeated, using oral doses that were prohibitively expensive and actually unavailable in the early days of penicillin. In addition to the repetition of original investigations, it has been necessary to evaluate many "new penicillins" as they became available.

Penicillin G (benzyl penicillin) was for a time the only type available commercially. Hence, for a time, the connotation of "penicillin therapy" was quite clear, but the situation is presently not so simple. There is a need for greater awareness and keener understanding of the differences between the "penicillins" that are currently available (Table 1). The differences are pharmacologic, toxicologic and therapeutic, and it is mandatory that therapy be more accurately defined in terms of the dose, the route of administration, and the type of penicillin employed. The glib statement that "The patient received penicillin therapy, but the infection failed to respond" has limited meaning, and if accepted uncritically may result in many unwarranted therapeutic failures and frank mishandling of some infections.

Pioneer investigators (2, 3) administered oral doses of 10,000, 20,000 and occasionally 50,000 units and were able to demonstrate only low and very transient penicillin plasma concentrations (penicillemia).[1] On the basis of studies carried

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[1] Penicillemia will be employed as the synonym for "penicillin plasma concentration."

TABLE 1
Penicillins

Common or Generic Name	Comments	Routes of Administration	
		Oral	Parenteral
Penicillin 'G' (sodium or potassium salt)	Safest and most universally applicable	+	+
Aluminum penicillinate	Insoluble* (1000 u/ml.)	+	−
Penicillin 'O'	Hypoallergenic	+	+
Penicillin 'BT'	Hypoallergenic	+	+
l-Ephenamine	Hypoallergenic (1000 u/ml.)	−	+
Penethemate	Preferential diffusibility	−	+
Benzathine (Also benzethacil or DBED penicillin)	Insoluble (200 u/ml. and tasteless)	+	+
Procaine penicillin	Insoluble (6000 u/ml.)	+	+
Benethamine	Insoluble (1000 u/ml.)	−	+
Hydrabamine	Insoluble (70 u/ml. and tasteless (16))	+	−
Penicillin 'V'	Insoluble (25) (700 u/ml.)	+	−
Ammonium penicillin	Insoluble (37)	+	−
Benzhydrylamine	Insoluble	+	−

* Refers to solubility in aqueous media.

out with these small penicillin doses, certain axioms with regard to orally administered penicillin arose and, regrettably, are still entertained as "fixed opinions" by many physicians. New data require that these "fixed opinions" be modified.

Reliability of oral penicillin

The original penicillin investigations were carried out with doses which seem ridiculously small in the light of current costs and supplies of penicillin but, because of the statements that were made on the basis of these studies, many physicians have doubts regarding the reliability of the orally administered drug. Because the small doses (10,000, 20,000 and 50,000 units) produced slight and very transient penicillemia, and in some cases none at all, the concept of "nonabsorbers" of penicillin came into existence. Under unique circumstances, an occasional patient may fail to absorb penicillin from the gastro-intestinal tract, but in the author's extensive experience no such patient has been encountered. When a dose of 100,000 units (or more) of penicillin has been administered by mouth, a penicillemia of variable duration has been demonstrated in *all* patients. When smaller oral doses have been administered, the antibiotic has been recovered in the urine, even when it has not been demonstrable in the plasma. The finding of penicillin in the urine is evidence of absorption from the gastro-intestinal tract, even though lack of demonstrable levels in the circulation may suggest "nonabsorption."

It has been shown repeatedly (4, 5, 6) that the *same* dose of penicillin administered to the *same* patients and under the *same* conditions gives rise to a

reproducible penicillemia. There are physiologic and pathologic differences between individuals, and the concentrations of penicillin as they are observed in the plasma over a period of time reflect these differences. This statement of variability of absorption of penicillin from the gastro-intestinal tract can be made with regard to many drugs, and physicians deeply interested in therapeutics would do well to focus attention on the vagaries of absorption of drugs other than penicillin and to individualize dosage schedules to an even greater degree than is presently the practice.

Acid and penicillin

In vitro it is readily demonstrated that acid destroys penicillin, and media of higher pH than 4 are increasingly deleterious. Hence, the thought of protecting penicillin with buffering agents was obvious, and sodium bicarbonate was employed by the original Oxford team of penicillin workers (2) as a means of accomplishing this objective. Whereas the Oxford investigators employed adequate quantities of alkalinizing material, the amounts of buffering substances ordinarily incorporated with penicillin are inadequate to neutralize any significant quantity of acid. If sufficient quantities of antacid (3 to 6 grams) are employed, penicillin can be protected during its passage through the stomach and higher degrees of penicillemia can be achieved (7). The use of such large quantities of antacid is obviously impractical, for imbalances of electrolytes may be induced in some patients. The role of antacids is therefore a limited one.

Food and penicillin

Food stimulates the outpouring of gastric secretions and the increasing of the pH of the stomach contents. Foods vary in their composition and accordingly there are differences in their ability to buffer the hydrochloric acid secreted into the stomach. Therefore, the influence of food is not entirely in the direction of increasing the pH of the gastric contents; it can have some protective effects. Not only do foods differ in their chemical composition but also in their physical characteristics. Hence, there may be a physiologic, biochemical, and mechanical influence of food upon the absorption of penicillin (8). Notwithstanding, experience and laboratory demonstrations dictate the oral administration of penicillin in the fasting or near-fasting condition in order to favor maximal absorption.

Insoluble penicillins

The protection of penicillin against destruction in the stomach has been attempted by various coatings and encapsulations, but these efforts have failed (9), for in the measure that these methods protected the penicillin they have also lessened the availability of the antibiotic for absorption from the gastro-intestinal tract. A number of metallopenicillins (aluminum, bismuth, and ferric salts) have been prepared, with the idea that insolubility might protect penicillin during its passage through the stomach. Aluminum penicillin, the best of these salts, is absorbed from the gastro-intestinal tract in amounts comparable to those observed after ordinary potassium penicillin G, but offers no advantage (4, 10). Procaine penicillin, so valuable as a repository penicillin for parenteral adminis-

tration, hydrolyzes rapidly in the volumes of fluid available in the stomach and gastro-intestinal tract and offers no advantage over potassium penicillin G (8) when administered by mouth.

Benzathine (benzethacil, DBED penicillin) is a highly insoluble penicillin. When administered *intramuscularly* it produces a low-grade penicillemia for weeks, but when administered orally, significant prolongation of penicillemia is not observed. By reason of insolubility, benzathine is relatively tasteless and can be presented in aqueous suspension for oral administration. The clinical advantage of the tastelessness of benzathine is counterbalanced by the fact that the penicillemia resulting from its administration is only a third or a quarter of that resulting from a similar dose of water-soluble potassium penicillin (11–14).

Until recently, the tastelessness of the oral suspension of benzathine was unique amongst oral penicillin preparations, but potassium penicillin has been suspended in anhydrous coconut and peanut oils to give highly palatable preparations. These oily suspensions of water-soluble penicillins induce penicillemias comparable to those following the use of tablets of the same penicillin and higher than those resulting from benzathine (14).

Other relatively insoluble salts of penicillin have been prepared, benethamine (6, 15), hydrabamine (16, 17), and benzhydrylamine (18), but they possess no advantage over potassium penicillin other than relative tastelessness. Indeed, the price of this tastelessness is a lower degree of penicillemia.

Hypoallergenic penicillins

Because penicillin is an antigen and numerous patients are exquisitely sensitive to it, efforts have been made in the direction of producing penicillins with less sensitizing potential. Specific examples of such penicillins are allylmercaptomethyl, "O", penicillin; butylthiomethyl, "BT", penicillin; and *l*-ephenamine. Although useful when parenterally administered and applicable to the treatment of some penicillin-sensitive patients, these penicillins have little to recommend them for oral administration (19). Malodorous breath develops promptly after the ingestion of either "O" or "BT" penicillin and persists for some hours.

Diffusibility

Chemists and microbiologists have altered the structure of the penicillin molecule and by so doing have attempted to accentuate certain desirable properties of penicillin. Penethamate (the diethylaminoethyl ester hydriodide of penicillin G) is a case in point and is noteworthy by reason of its interesting diffusibility into pulmonary, lymphatic, and nervous tissues (20, 21). Regrettably, this diffusibility, which is a highly desirable property of an antibiotic agent, is accompanied by an increased toxicity (22). When administered by mouth, penethamate is less well absorbed from the gastro-intestinal tract than penicillin G (5). Penicillin V (phenoxymethyl penicillin), known as a chemical entity for some time, has only recently been reported to have interesting properties of insolubility, stability in the presence of acid, and better diffusion from the gastro-intestinal tract into the circulation (1, 23–25).

Penicillin and renal excretion

Of all the penicillins which have been studied, none has been shown to be superior to potassium or sodium penicillin G in terms of giving a prompt and predictable penicillemia.[2] Further, the suspension of potassium or sodium penicillin in anhydrous coconut or peanut oil has overcome the one disadvantage of taste which existed heretofore. In whatever form penicillin is administered by mouth, and has been absorbed into the circulation, the antibiotic is rapidly excreted by the renal tubules (26). Since it may be assumed that an antibiotic is of service therapeutically only while it is circulating in the body, attempts have been made to retain penicillin in the body for longer periods of time by inhibiting physiologically and reversibly this tubular secretion of penicillin (27–30). The best of the agents employed for this purpose is probenecid (*p*-(di-*n*-propylsulfamyl)-benzoic acid), and by the administration of probenecid orally in combination with penicillin the resulting penicillemia can be increased two to four-fold, regardless of the type of penicillin that is administered, the route of its administration or the dose administered (5, 6, 11, 30).

In the laboratory, at least, it has been possible to produce a penicillin with a "built-in" deterrent to renal tubule secretion, *p*-amino benzyl penicillin (31). It is a hope, therefore, that the microbiologists and chemists may yet confer upon the penicillin molecule the properties of diffusibility through the gastro-intestinal mucosa and slower excretion by way of the renal tubules. If either or both of these goals are achieved, the usefulness of penicillin administered by the oral route will be tremendously extended.

Oral penicillin versus intramuscular penicillin

According to one of the axioms that emerged from the early penicillin investigations, it was necessary to administer orally five to ten times the intramuscular dose in order to attain equivalent penicillin plasma concentration (32). This "rule of thumb" has been affirmed many times, and a confirmation of the statement may be seen in Figure 1. Graded doses of penicillin administered orally and parenterally to the same patients show that the increments in dosage are reflected predictably in the grades of penicillemia. One million units of orally administered penicillin produces approximately the same peak of penicillemia as that observed after the intramuscular administration of 200,000 units—one-fifth as much. With the currently available quantities of penicillin, which make possible the administration of "grams" daily by the oral route, there can no longer be any question that the same degrees of penicillemia can be achieved by oral administration as by parenteral administration of doses of penicillin which have long been acknowledged to have full therapeutic effectiveness.

Procaine penicillin administered by the *parenteral* route is efficacious when it is administered once or twice a day in doses of 300,000 units. The usual penicillin plasma concentration resulting from doses of this magnitude approximates 1 to 2 units within an hour or two of injection and declines slowly over 18-hour

[2] Phenoxymethyl, "V," penicillin may prove to be the exception, but sufficient data are not yet in hand.

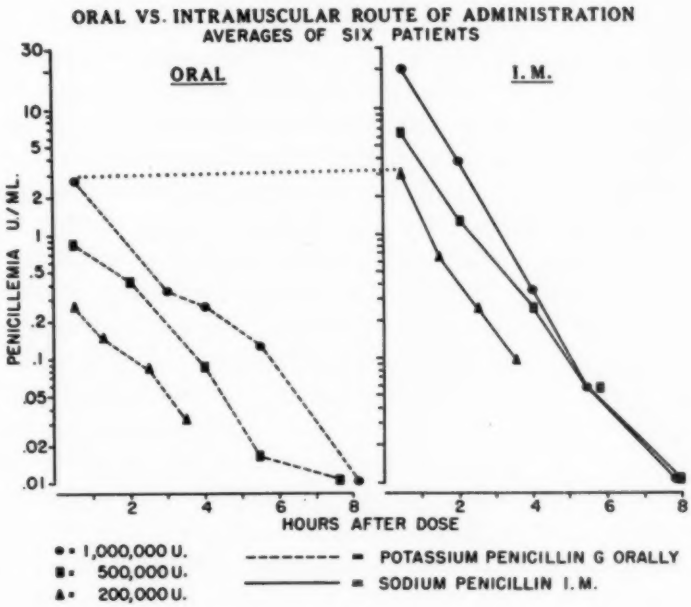

FIGURE 1

to 24-hour periods to 0.03 unit or less. Such doses of parenteral penicillin have been shown repeatedly to have full therapeutic effect for most of the commonly occurring infections. The same magnitude of peak and maintained concentrations of penicillin can be attained by the *oral* administration of three times as much penicillin (33) (1,000,000 units in divided doses in combination with probenecid). Thus, by the use of an agent capable of inhibiting, physiologically and reversibly, the renal tubular secretion of penicillin, it is possible to modify the rule of thumb of "five to ten times the parenteral dose administered by mouth" to a "three-fold" dictum. On the basis of the laboratory demonstration of circulating antibiotic, it seems reasonable to assume that these two schedules of dosage will have comparable therapeutic effectiveness.

Actually, the axiom of five to ten times the parenteral dose administered by mouth in order to obtain an equivalent degree of penicillemia should be restricted to a discussion of water-soluble potassium or sodium penicillin. It is possible with some of the insoluble penicillins (procaine penicillin, benzathine and benethamine) to attain higher peak concentrations in the plasma following orally administered doses than following parenterally administered doses of the same penicillins (6). These facts emphasize the necessity of qualifying statements about penicillin with regard to the type, the route of administration, and the size of the dose.

THERAPEUTIC IMPLICATIONS

There may be some skeptics who are inclined to dismiss the foregoing data as mere laboratory demonstrations, without significance as far as therapy is concerned. Perhaps another look backward to the early days of penicillin may serve to present these data in their proper therapeutic light. In 1943 a report on peni-

cillin was drawn up for the National Research Council, and a passage from this report is worthy of quotation (34). "Patients with pneumococcic pneumonia frequently recover following the use of *100,000 units given over a period of three days.* This is especially important in sulfonamide-resistant pneumococcic infections. It may be necessary to give between 60,000 and 90,000 Oxford units daily for four to seven days to get a maximum effect." Thus, a parenteral dose of 30,000 or 40,000 units of penicillin per day was sufficient to transform a lethal disease like pneumococcal pneumonia into a readily controlled infection. This daily quantity of penicillin was administered either as 5,000 units intramuscularly every three hours, or 10,000 units every four hours. Since such schedules of therapy were unquestionably therapeutically effective, it is of interest to estimate the magnitude of penicillemia that might have been obtained when these schedules were employed. In Figure 2 are presented the penicillin plasma concentrations resulting from the intravenous and intramuscular administration of 10,000 units of penicillin, as reported in 1943 (3), compared to those resulting from the oral administration of 200,000 and 400,000 units respectively of potassium penicillin administered orally (5). It seems clear that the penicillemia induced by a reasonable schedule of orally administered penicillin exceeds that induced by an intramuscular schedule of dosage that is known to be therapeutically effective.

It may be argued by some that the character of pneumonia has changed over the years and the small parenteral doses of penicillin referred to would no longer be effective in the handling of pneumococcal pneumonia. Actually, in 1950 a series of pneumococcal pneumonia patients was treated according to a dosage schedule of 5,000 units of penicillin administered intramuscularly every three

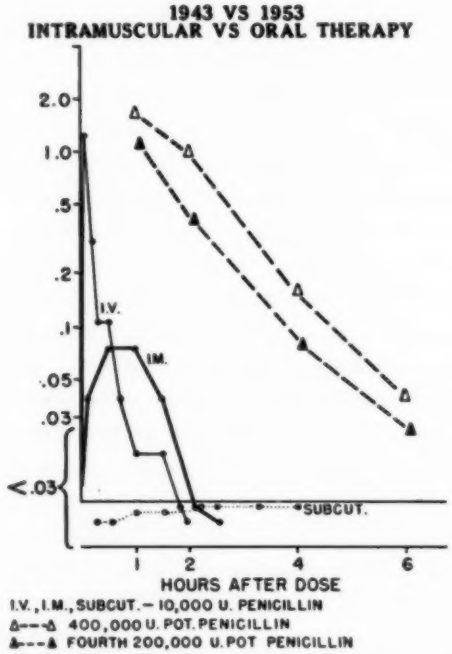

FIG. 2. (The i.v., i.m., subcut. data are adapted from Rammelkamp and Keefer (3).)

hours, and excellent therapeutic results were obtained (35). Penicillin-resistant pneumococci have not been observed, and pneumococcal pneumonia continues up to the present to be an infection readily treated with penicillin.

Many infections have been successfully treated with orally administered penicillin and the degrees of penicillemia attained with reasonable schedules of orally administered antibiotic have been the same as those observed with therapeutically proven parenteral schedules. There appear to be no reasonable grounds for reluctance in employing orally administered penicillin for the handling of most penicillin-treatable infections.

Some physicians dismiss the importance of penicillin plasma concentrations, arguing that infections can be treated without the necessity of achieving or attaining demonstrable penicillin plasma concentrations. Those who take this point of view base their argument on the ease with which gonorrhea and pneumonia can be treated with penicillin. Such infections (uncomplicated) can be treated with little or no measurable quantities of antibiotic circulating in the plasma. The fallacy of the "dismissal" of sustained penicillemia as being unimportant is that one is not treating an infection in the blood stream but in the parenchyma of various organs of the body. It is in these infected tissues that it is necessary to have effective concentrations of chemotherapeutic agents. In order to attain this objective it is purposeful to maintain concentrations in the plasma that exceed by five and ten times the concentrations necessary to inhibit *in vitro* the infecting organisms. The necessity of approximating this criterion in order to achieve success in treatment is established *not* by the studies carried out with easily treated infections but by the handling of problem cases such as subacute bacterial endocarditis and meningitis. There is merit in maintaining demonstrable plasma concentrations of penicillin, even though one is treating an infection which is extremely vulnerable to attack with penicillin, in order to *insure effective quantities of the antibiotic at the sites of infection*. The questionableness of relying upon a therapy that assures a constantly demonstrable but minimal penicillin plasma concentration has been demonstrated by the attempt to trest pneumococcal pneumonia with a single intramuscular injection of 300,000 units of benzathine (36).

CONCLUSIONS

Penicillin is preeminent amongst the presently available antibiotics. Although the first of the great antibiotics, it has been the last to be accepted as being effective when orally administered.

Penicillin is presently available in a number of chemically modified forms, and each of these has been critically compared to water-soluble sodium or potassium penicillin. On the basis of an extensive experience, it is concluded that:

(a) Sodium or potassium penicillin G produces the most prompt and highest penicillemia of any presently available form.

(b) Sodium or potassium penicillin can be rendered flavorsome by suspension in anhydrous coconut or peanut oil.

(c) In an oral dose of 1,000,000 units, sodium or potassium penicillin produces

a penicillemia comparable to that resulting from the intramuscular injection of 200,000 units of water-soluble penicillin.

(d) Oral penicillin in reasonable dosage (200,000 units administered three or four times a day) can induce penicillin plasma concentrations greatly in excess of those shown to be effective therapeutically and resulting from an intramuscular injection of 10,000 units of potassium penicillin every four hours.

(e) Combining probenecid with orally administered penicillin enhances plasma penicillin concentrations two to four times, so that the maintained penicillemias are comparable to those following the parenteral administration of repository penicillins.

(f) Orally administered penicillin is applicable to the therapy of most of the commonly occurring penicillin-treatable infections. It is anticipated that chemical modification of penicillin will build into the molecular structure physical properties that will greatly extend the use of oral penicillin.

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CURRENT CONCEPTS IN THE MANAGEMENT OF PULMONARY TUBERCULOSIS*

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Without meaning to minimize the laudable accomplishments of the pioneer phthisiologists, it is only fair to concede at the outset that the past decade has probably witnessed more real progress in the management of tuberculosis than have all of the preceding years put together. In fact, one need go back even less than a decade to the time when nothing but bed rest and assorted methods of pulmonary collapse were available for the treatment of pulmonary tuberculosis. Then within the compass of a very few years, the advent of antimicrobial therapy, and with it the exploitation of the potentialities of excisional surgery, revolutionized the management of this disease. From an uninteresting and basically unchanging topic, the subject of tuberculosis therapy was converted to a complex and fascinating story, one still in a state of flux but of proven effectiveness and of sufficient interest to justify this resumé.

CHEMOTHERAPY

The first inkling that we might eventually secure an effective chemical agent against the tubercle bacillus was afforded in 1938 by the work of Rich and Follis (1) who demonstrated that *sulfanilamide* exerted a limited suppressive effect on experimental tuberculosis in guinea pigs. This was promptly confirmed by Feldman and Hinshaw who, after continuing to study the antituberculous effectiveness of various other drugs during the early '40s, were in an ideal position to evaluate streptomycin upon its discovery in January 1944. Following its demonstrated effectiveness in animals, clinical appraisal was begun in December 1944, in collaboration with Pfuetze, and by 1947 the usefulness of streptomycin in the treatment of tuberculosis had been indisputably established. The historical aspects of this period in the development and evaluation of streptomycin have been described in fascinating fashion elsewhere (2, 3, 4). Subsequently, as a result of large-scale clinical studies conducted by the Veterans Administration, the proper dosage, the optimal duration of therapy and the advisability of combined drug administration were studied in an effort to obviate toxicity, delay the emergence of resistant strains of tubercle bacilli and prevent relapse.

Early investigations of *streptomycin* demonstrated that the tubercle bacillus quickly grew resistant to streptomycin administered alone. While trying to ascertain whether the simultaneous administration of a second bacteriostatic drug along with streptomycin might provide some synergistic benefit, it was

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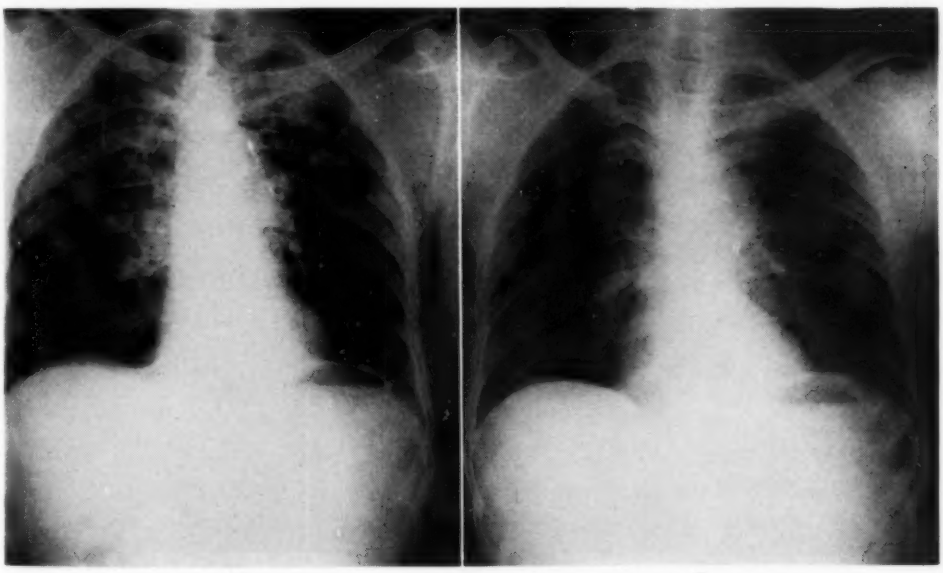
discovered rather fortuitously that combined therapy seemed to delay markedly the development of bacterial resistance. Because of this, the combination of streptomycin and *para-aminosalicylic acid* (PAS) emerged as the regimen of choice, the PAS permitting almost unlimited prolongation of streptomycin administration without the development of resistance. Just why this remarkable phenomenon occurs is unknown and seems all the more amazing, when one considers that PAS per se is a relatively weak chemotherapeutic agent.

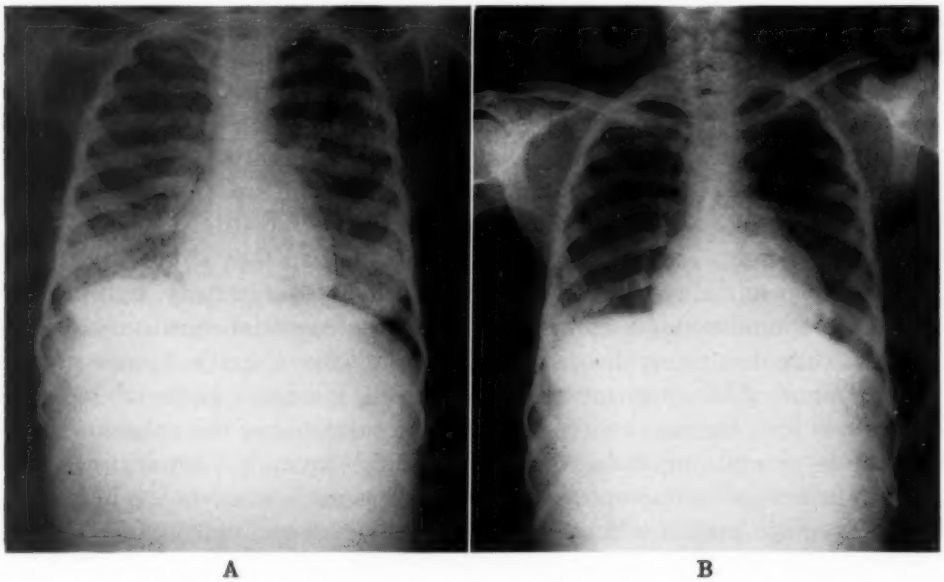
Other refinements soon followed. Thus it was shown that streptomycin given twice weekly was no less effective than when it was given daily, and possessed in addition the advantages of further prolonging bacterial sensitivity to streptomycin, while decreasing the danger of accumulative toxicity. Moreover, it became apparent that interruptions in treatment increased bacterial resistance. One gram of streptomycin twice weekly is now accepted as the optimum dosage. As for PAS, no optimum dosage has been decided upon, but the ingestion of 12 grams daily has gained acceptance simply because it represents the largest dose that the average patient will tolerate.

Because of the toxic effect of streptomycin on the eighth cranial nerve, especially the vestibular division, an attempt was made to substitute dihydrostreptomycin but, curiously enough, this proved toxic for the auditory division and was therefore practically abandoned. The combination of streptomycin and dihydrostreptomycin in half proportions, for the purpose of obtaining the therapeutic effect of both while avoiding the toxic effects of either, is still in the process of being evaluated but appears to hold some promise for long-term administration (5).



A B

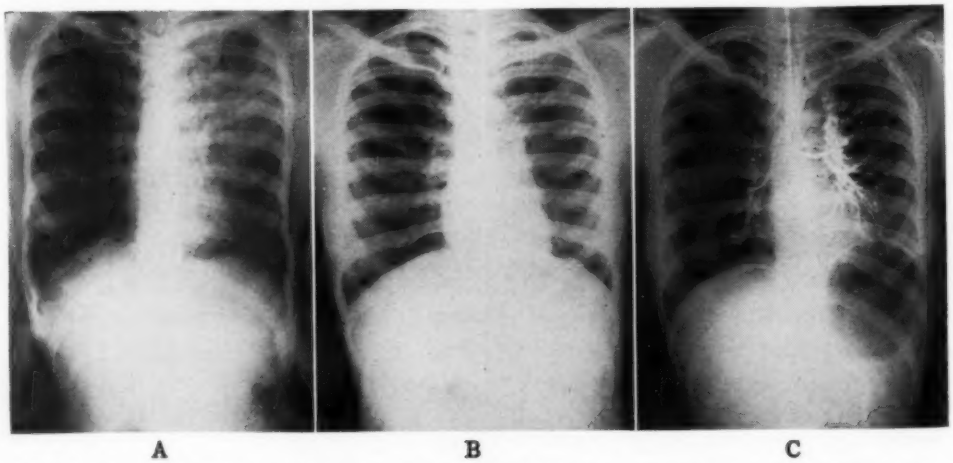
FIG. 1. Chest of a 68-year-old colored man. (**A**) Roentgenogram showing bilateral caseonodular tuberculosis. Following intermittent streptomycin and daily PAS therapy there was prompt improvement. (**B**) Film twelve months later showing complete clearing. The patient remains well.



A B

FIG. 2. Chest of a 22-year-old colored girl, severely ill with acute hematogenous tuberculosis as shown by initial roentgenogram (**A**). Treatment consisted of daily streptomycin and PAS. (**B**) Roentgenogram six months later demonstrating complete resolution. The patient continues to do well.

The one thing that has not been accurately determined is the optimum duration of therapy. In view of the chronicity of tuberculosis, the tendency for necrosis and the fact that the drugs so far available are tuberculostatic and not tuberculocidal, it is easy to understand why chemotherapy must be maintained for long periods of time before healing can be achieved. This has been made possible only by giving streptomycin and PAS in combination (Figs. 1, 2 and 3). In order to



A B C

FIG. 3. Chest of a 20-year-old colored girl whose initial roentgenogram (**A**) showed severe left caseopneumonic tuberculosis with cavitation. Almost complete clearing ensued during intermittent streptomycin and daily PAS therapy. (**B**) Roentgenogram after four months of treatment. However, because of persistently positive sputum, a bronchogram (**C**) was made revealing severe bronchiectasis, for which a left pneumonectomy was performed.

determine how long chemotherapy should be maintained, an elaborate study of the so-called "target-point lesion" is now under way.

To be so designated, in other words to have reached the target point, a lesion must be stable radiographically, all cavities must be closed upon x-ray examination (including planigrams), and the sputum must be consistently negative for acid-fast bacilli by culture (6). From past experience we know that the interruption of chemotherapy before lesions reach the target point is likely to be followed by relapse. What must be determined is the amount of chemotherapy necessary to assure the stability of target-point lesions. Until now it has been customary to continue chemotherapy until the disease can be classified as inactive, that is, for six months after it meets the requirements for a target-point lesion.

Since its availability in May 1952, *isoniazid* in 300-mg. daily dosage has provided convincing proof of its right to equal rank with streptomycin and PAS. As with streptomycin, bacterial resistance quickly develops when isoniazid is given singly, but is considerably delayed when given either with streptomycin or PAS. Preliminary evidence suggests that all three possible combinations, *viz.*, streptomycin and PAS, isoniazid and PAS, and streptomycin and isoniazid, have comparable effectiveness. A unique and particularly encouraging aspect of isoniazid is its ability to penetrate deeply into necrotic foci. It also presents toxic manifestations but, except for peripheral neuritis and toxic encephalopathy, these are seldom serious.

During the past year there has been mounting evidence that *pyrazinamide* (aldinamide) and isoniazid administered concurrently exert antituberculous activity of a sort superior to previous combinations (7–10). Indeed, results of animal experiments suggest that this combination may be as close to a true tuberculocidal agent as has yet been achieved (7). Until the question of toxicity is settled, and that refers mainly to hepatitis, the general use of the pyrazinamide-isoniazid combination cannot be advocated, but we suspect nonetheless that in time this combination will prove of immense value.

Terramycin is a satisfactory substitute for PAS but its high cost precludes its routine use. When resistance to the front-line drugs develops, both terramycin and viomycin may become quite useful, but in the case of viomycin the high toxicity and comparatively low level of effectiveness combine to prohibit any important contribution by this drug. Tibione, a thiosemicarbasone derivative, has shown nothing to justify the initial enthusiasm it stimulated and need not be further considered here. The same is true of any number of other ineffective agents.

ADJUNCTIVE THERAPY

Although chemotherapy is the keystone in the treatment of pulmonary tuberculosis, there are a number of adjunctive measures which deserve comment.

Bed rest has always been considered essential in the management of the tuberculosis patient. In the acute phase there can be no questioning its importance, for it will reduce fever, diminish the cough and expectoration, quiet the pulse and improve the appetite. Without complete rest at this stage, symptoms will be aggravated and the disease may continue to spread.

Conversely, once symptoms disappear and chemotherapy is well under way,

there would seem to be no advantage to strict bed rest. Certainly any extreme rigidity of attitude can be relaxed. As Waring has put it, "Bed rest is good medicine but like every other good medicine, has its optimum dosage. In too large doses it is a destroyer of morale, an instigator of rebellion and defeats its purpose. In too small doses it is equally dangerous" (11).

Collapse procedures were once the backbone of any hospital program for the management of tuberculosis. Now they have a much smaller field of usefulness. Artificial pneumothorax, for example, is so fraught with complications such as a nonexpandible lung and tuberculous empyema that it has largely been abandoned. In selected cases under chemotherapy it may rarely be justified.

Pneumoperitoneum is likewise a procedure of dubious merit. It is, indeed, an easy, reversible method but the impression in some quarters that this is an effective form of therapy is no more than an impression, for it is not substantiated by any controlled study. Statistical proof of its value is particularly difficult to ascertain, inasmuch as the patient almost invariably is also receiving chemotherapy.

Crushing the phrenic nerve to obtain elevation of the appropriate leaf of the diaphragm is likewise of questionable value and is seldom indicated nowadays.

Unlike other methods of collapse, thoracoplasty remains a good procedure with a high rate of cavity closure in properly selected cases. With modern physiotherapy it need not be particularly deforming. Although the mortality rate is less than that with resection, there has been a very definite trend away from thoracoplasty and toward resection. Admittedly, the results with resection are generally superior, but because of the very low mortality rate with thoracoplasty, there is little likelihood that the latter procedure will ever be completely replaced by resection. Extraperiosteal plombage with some plastic material such as lucite spheres is likewise useful in selected instances, but entails the added risk of infection secondary to the use of a foreign body.

Prior to the streptomycin era excisional surgery was rarely utilized in the treatment of tuberculosis because of the extremely high rate of spread, reactivation and bronchopleural fistula accompanying its use. Under streptomycin coverage it was found that the complication rate was tremendously reduced, with the result that the application of resections has paralleled the improvements in chemotherapy. Various situations have evolved which are now deemed indications for resection. The less controversial ones include thick-walled cavities, lower-lobe cavities, tuberculous bronchiectasis, irreversible bronchostenosis, so-called destroyed lung, and thoracoplasty failures.

Since 1946 there has been a continually changing attitude in the use of chemotherapy in relation to surgery. Originally the emphasis was upon protection for surgery. Subsequently, more and more patients were enabled to become candidates for surgery only as a result of prolonged chemotherapeutic regimens. In essence, surgery has come to be used for the removal of disease that chemotherapy cannot be expected to heal. In the case of open cavities viable bacilli can usually be recovered, even after prolonged medication. In closed necrotic foci, on the other hand, it has been difficult to culture organisms, even without preliminary chemotherapy. For this reason there has been considerable controversy about the need for excision, based on the reasoning that the organisms, though

visible in specially stained tissue sections, do not grow in cultures and are, therefore, presumably dead. This is probably one of the leading questions at present and is currently being investigated. Preliminary reports by Hobby and her coworkers (12) suggest that organisms can actually be recovered from closed necrotic lesions, if special cultural methods are used. In some instances it has taken over six months for the organisms to appear in cultures! Further results of this sort will point to the hazard inherent in these closed cavities and provide justification for their surgical removal. In any event surgery will continue to be an invaluable part of the overall treatment of tuberculosis until such time as a true bacteriocidal drug becomes available.

In conclusion, one must emphasize, not too tritely it is hoped, that the secret to the successful management of the patient with pulmonary tuberculosis lies not in any one drug, nor in any one surgical feat, nor in any one therapeutic dictum, but in the carefully planned and integrated use of all these many measures under the joint supervision of the internist, bacteriologist and surgeon working with the closest possible coordination.

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MECHANISM OF ABSORPTION AND ANTIGENICITY OF ABSORBABLE COLLAGEN SUTURES*

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The only absorbable suture material now available is derived from the submucosa of the sheep's intestine. Being a biologic product, it is subject to all the biologic variations inherent in such material. Over the past decade, numerous investigators have attempted to make synthetic absorbable suture material. As part of our program in developing such a suture, it was felt necessary to examine the mechanism by which our presently available products are absorbed. An understanding of tissue reaction to, and the mechanism of absorption of the material which has proved satisfactory is necessary as a base line for comparison of new materials. Furthermore, such information throws light on factors involved in the proper clinical use of such sutures.

This report merely summarizes the results of some three years of study on this subject. Details will shortly be published.

The tissue reaction to catgut was compared with the reaction to absorbable sutures derived from beef serosa. Since no significant difference in histologic reaction was noted after implantation of collagen sutures from these two sources, the results were combined for presentation.

Although there are numerous publications dealing with tissue reactions to catgut, it does not appear profitable at this time to review this extensive literature. The difference in methods and materials used in the older studies makes comparison with present work hazardous, if not impossible.

ABSORBABILITY OF CATGUT—TISSUE REACTION

Studies on the absorbability of catgut sutures and the tissue reactions occasioned by their implantation were made on 211 albino rats, 90 rabbits, 23 guinea pigs and 47 mongrel dogs. Sterile sutures were implanted in these animals under the usual aseptic technics. Since the site of implantation undoubtedly makes a difference in the rate at which sutures are absorbed, all implantations were made into muscle tissue. From 2 to 12 sutures were implanted in each animal under aseptic technic. Histologic observations were made at various intervals ranging from five to one hundred days, depending upon the species and the results of preliminary gross observations.

In evaluating the degree of tissue reaction observed in any microscopic section, the following factors were considered: An estimation was made of the number of each of six cell types (mononuclears, neutrophils, eosinophils, lymphocytes, fibroblasts and giant cells) per oil immersion field, and for each of the six cell types

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a grade was obtained, which corresponded to the number of cells counted per high power field. These grades, varying from 1 to 8, corresponded to cell counts of from 1 to 150 per microscopic field. The overall density of the total inflammatory reaction was estimated and grades ranging from 1 to 8 were assigned, based upon this estimate. Empirical weighting factors were assigned to the various cell types. Thus, the final numerical contribution of each cell type to the total grading of the overall tissue reaction was obtained by multiplying the grades of that type by the assigned weighting factor. Although this grading system seems to be complicated and subject to considerable variation, depending upon the judgment of the observer, it has been found that different observers who are experienced in this method seldom differ in their evaluation of a given section by more than 1 grade unit.

As might be expected, the rat showed most rapid absorption of catgut sutures, the rabbit was next and the dog showed the slowest absorption. For instance, plain catgut sutures (size 2/0) were completely absorbed in the rat in twenty-five days (Fig. 1). The same suture showed no evidence of absorption in the rabbit in the first fifteen days; thereafter, absorption was fairly rapid and was complete at the end of about fifty days. In the case of the dog, absorption was only about 50 per cent complete at the end of sixty days. Also, as to be expected, chromic sutures were absorbed more slowly than plain sutures. In the rat, chromic sutures were not completely absorbed until after the sixtieth day. In the rabbit, complete absorption of the chromic sutures occurred shortly after the seventy-fifth day (Fig. 2), but in the dog only about 40 per cent of the suture was absorbed after seventy-five days.

It was also found that the type of tissue reaction observed with implanted

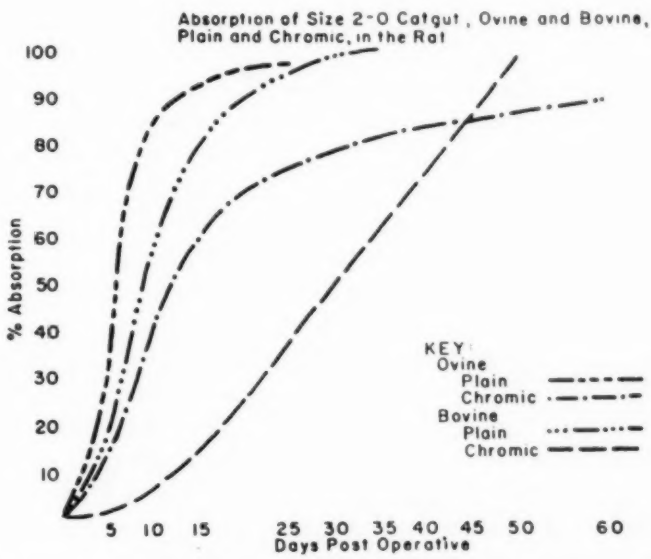

FIG. 1 (Reproduced with permission of the publisher from Sewell, W. R.; Wiland, J., and Craver, N.: A new method of comparing sutures of ovine catgut with sutures of bovine catgut in three species, *Surg., Gynec. & Obst.* **100**: 483 (Apr.) 1955.)

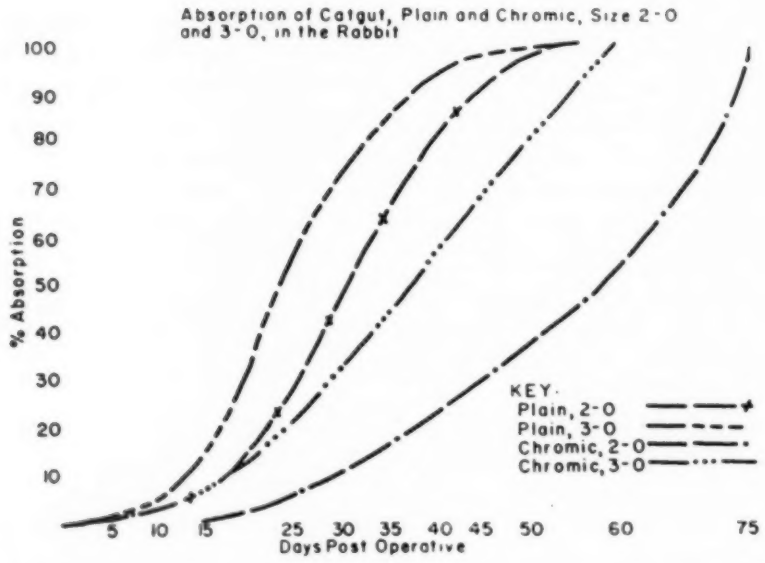

FIG. 2 (Reproduced with permission of the publisher. *See* Figure 1 for reference.)

catgut sutures varied with the species. In the rat, the initial reaction, five days after operation was inflammatory, with edema, fibroplasia and the accumulation of many polymorphonuclear leukocytes over a wide area. The reaction had subsided considerably by the tenth day, when lymphocytes began to predominate. Thereafter the infiltrating cells were principally lymphocytes, mononuclears and giant cells, and there was coalescence and disappearance of the fibrous tissue originally laid down. The inflammatory reaction noted in the rat was such that possible infection was suspected. However, repeated cultures failed to reveal any viable micro-organisms.

In the rabbit, the reaction to any type of absorbable suture consisted initially of a few fibroblasts and some lymphocytes. The lymphocytes usually increased in number until digestion was well under way. Their later decrease was followed by an increase of mononuclears and occasional multinucleated giant cells. Generally, the greatest tissue reaction occurred when absorption was about 50 per cent complete, after which it subsided considerably.

In general, the tissue response in the dog to any size of plain catgut seemed to be greatest at about the fifteenth postoperative day. Reactions at this time were predominantly of the chronic inflammatory type, with lymphocytes, mononuclears, fibroblasts and occasionally polymorphonuclear leukocytes. All elements appeared to decrease in number thereafter. However, there was appreciable variability in the response of individual animals within a species. The variations were the greatest in the dog and it is concluded that the dog is the least satisfactory experimental animal for the study of comparative absorbability and tissue reaction produced by different kinds of sutures.

As has been noted by other observers, plain sutures occasioned a significantly greater tissue reaction than did chromic catgut sutures. This fact is not always

appreciated by surgeons. It was also observed that the rate of absorption of catgut sutures appeared to be directly proportional to the number of polymorphonuclear leukocytes present and surrounding the implanted suture. Since this type of reaction predominated in the rat, it is not surprising that sutures were absorbed more rapidly in the rat than in the other species studied. As it has been well established that leukocytes are rich in proteolytic enzymes—particularly the polymorphonuclear leukocytes—these observations suggest that at least part of the mechanism of absorption of catgut is related to hydrolysis of collagen by leukocytic enzymes. This also provides a logical explanation for the observation that local infection with its concomitant polymorphonuclear leukocytosis markedly hastens catgut absorption.

LOSS OF TENSILE STRENGTH OF CATGUT *IN VIVO*

In a second series of experiments, the tensile strength of 615 specimens of 2/0 plain and chromic catgut of bovine origin was compared with that of 673 specimens of 2/0 plain and chromic gut of ovine origin in 123 rats, 57 rabbits and 12 dogs. For this study strands of suture were divided into alternate 5-inch and 8-inch lengths and implanted under aseptic conditions into the subcutaneous tissues of the animals being studied. The strength of the 8-inch strands was determined immediately. The ends of the 5-inch strands were dipped several times in collodion until uniform coats could be seen on each terminal inch. This technic was used to avoid digestion of the ends of the suture, which must be inserted into the clamps of the apparatus used for testing tensile strength. After drying, the sutures were implanted, using aseptic technics. All animals were given 150,000 units of procaine penicillin intramuscularly immediately following the implantation of sutures, in order to avoid possible infection. Selected animals were killed at various intervals after implantation and the sutures removed. The

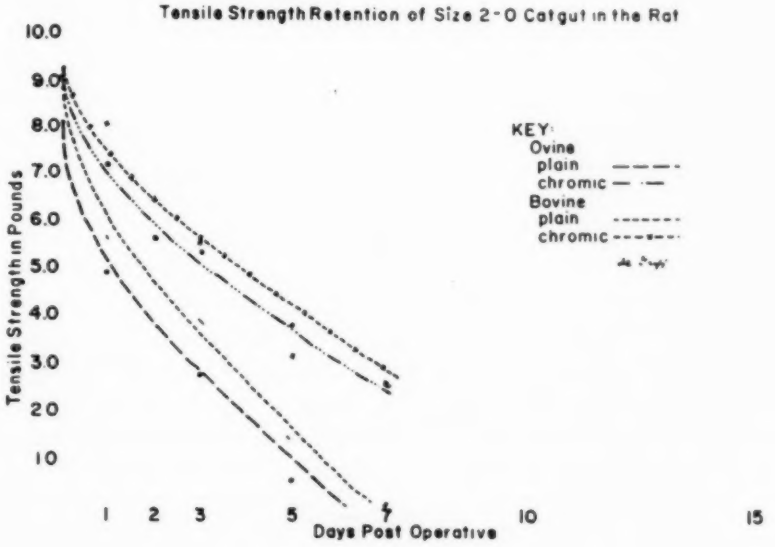

FIGURE 3

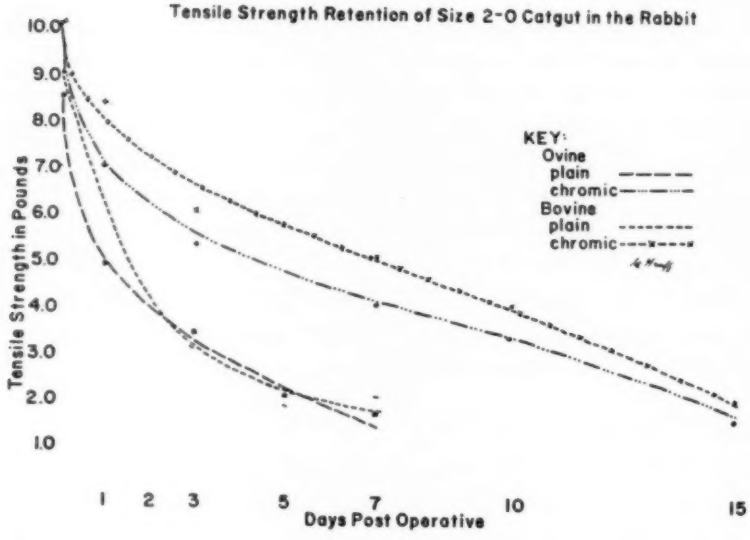

FIGURE 4

collodion ends were inserted immediately into the clamps of the Scott tester and the tensile strengths determined. Under this arrangement the occasional suture that broke at the clamp was omitted from later calculations, on the assumption that the clamp had injured and weakened it.

It should be noted that these sutures were not implanted under tension and therefore the rate of loss of tensile strength was probably higher than that which would be observed under more normal conditions of use. It has been found that sutures under tension resist enzymatic attack *in vitro* to a much greater extent than do sutures which are not subjected to tension.

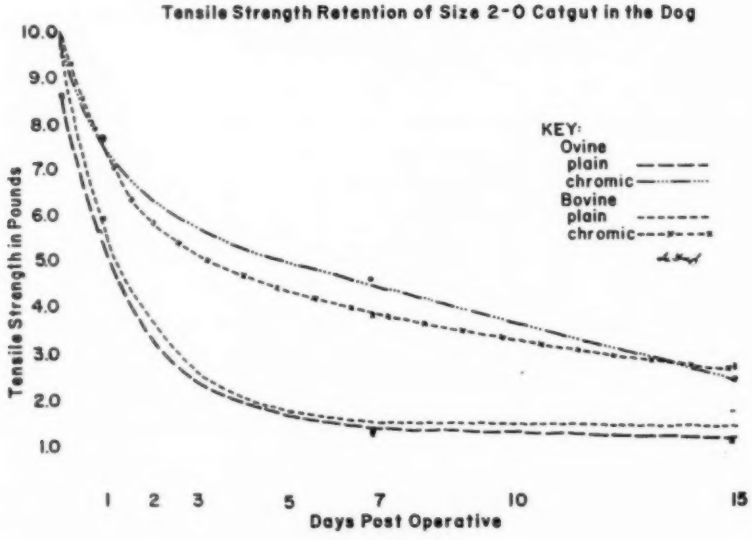

FIGURE 5

The rate of loss of tensile strength was observed to be more rapid in the rat than in the rabbit and the dog (Figs. 3, 4 and 5). There was no significant difference between the rate of loss of tensile strength between the rabbit and the dog. This observation is in line with the more rapid absorption of the catgut sutures in the rat. Chromicized catgut, whether of bovine or ovine origin, was always stronger than plain catgut and lost its tensile strength more rapidly. Relatively, the rate of loss of tensile strength of chromicized catgut was two to three times slower than that of plain gut. In the three species of animals about half of the original tensile strength of the plain sutures was dissipated within two days, whereas for the chromic gut, the time required to lose half the strength was about four days. The relatively large amounts of tensile strength lost during the first twenty-four hours agrees with results of other investigators. As will be shown later, this early rapid initial loss of strength is due to factors which have not heretofore received too much attention.

Although sutures made from beef serosa generally appeared to have significantly superior initial tensile strength, there seemed to be no difference in the rate of its loss in any species between catgut made from beef serosa and catgut made from the conventional sheep submucosa.

MECHANISM OF ABSORPTION

The rapid loss of tensile strength of sutures during the first twenty-four hours hours after implantation appeared to us to be due to some mechanism other than digestion by tissue enzymes. Since it is known that hydration of collagen greatly weakens this material, it seemed possible that hydration within the tissues might explain the rapid loss of tensile strength which we observed. To test this hypothesis, sutures were exposed to physiologic saline in a buffered medium at three different pH's—5, 7 and 9. Tensile strength determinations were made at frequent intervals.

Plain sutures kept in saline at pH 5 lost approximately 50 per cent of their tensile strength after seven days. At pH 7 the loss at seven days was in the neighborhood of 45 per cent. At pH 9 the loss was so rapid that from 57 to 61 per cent of the original strength disappeared during the first day of immersion. Chromic catgut, as might be expected, appeared to hydrate less rapidly. At the end of twenty-five days at pH 5, approximately 62 to 66 per cent of the original tensile strength remained. At twenty-five days at pH 7, 58 to 63 per cent of the original strength remained but at pH 9 the proportion was only 19 to 21 per cent.

It is obvious from these figures that a medium slightly on the acid side is more favorable for retention of tensile strength of catgut than a neutral or alkaline medium. The rapid loss of strength is due primarily to hydration, which breaks the hydrogen bonds of the collagen molecule. Thus, the early loss of tensile strength in tissue is most likely related to hydration and not to enzymatic activity. This is borne out by the observation that in the first few days after implantation when the sutures have lost much of their original tensile strength, no evidence of loss of structure can be observed. Later loss of tensile strength, after several days of implantation, appears to be directly related to the density of

polymorphonuclear leukocytes present around the suture. This loss is probably due to enzymatic activity affecting the peptide bonds of the collagen molecule.

A chance observation led us to investigate another factor that appears to be a cause of rapid loss of tensile strength of catgut sutures *in vivo*. One method of testing absorbability *in vitro* is to incubate catgut sutures in a medium containing proteolytic enzymes such as trypsin or papain. On one occasion our temperature controls on the incubator failed and the temperature rose from 37° to 41°C. The sutures were digested about five times more rapidly than normal. This suggests that postoperative fever can play a role in early absorption of catgut sutures.

SENSITIZATION TO CATGUT

Numerous reports in the literature have been presented tending to indicate that catgut may be a cause of sensitization and that subsequent implantations of sutures may result in wound disruption or severe local tissue reactions. Many of these papers were published from ten to twenty years ago and the materials used were far less pure than those available today. It was thought worthwhile to test present-day catgut for its ability to sensitize, utilizing the Freund and McDermott technic in guinea pigs. Suspensions of catgut mixed with killed tubercle bacilli were injected. After a suitable interval, challenging doses of a suspension of the same catgut material were injected intravenously into the presumably sensitized animals. In no instance was anaphylaxis observed. Similar tests were conducted, utilizing the sensitized isolated uterus of the guinea pig. In no instance was a contraction observed from introduction of catgut suspension into the bath. On the other hand, similar uteri sensitized to horse serum showed the typical allergic response upon introduction of horse serum into the bath.

To test whether local tissue sensitivity could be induced by catgut, animals sensitized by the Freund-McDermott technic were exposed to implantation of suture material. Tissues were removed, sectioned and studied microscopically. Grossly, no difference could be seen between sensitized and control animals. However, upon microscopic examination it was found that a significantly greater number of eosinophils appeared to surround the sutures in the sensitized animals. This suggests that a slight local tissue sensitivity was produced. Since reinforcement technics had to be used to sensitize these animals and since the reaction was microscopic and consisted merely of an increase in the number of eosinophils, it appears unlikely that sensitization to catgut is an important clinical factor today. This is borne out further by the fact that evidence exists to suggest that proteins which do not contain aromatic amino acids are incapable of causing sensitization. Collagen contains little, if any, of the aromatic amino acids. Catgut sutures used in this work were assayed for their content of collagen; it was found that the sutures contained between 96 and 97 per cent collagen, the remaining material being mostly lipid. There is always the possibility that a small trace of sheep-muscle protein was present, and this could easily account for the slight degree of sensitization which was noted. Attempts are now being made to prepare 100 per cent pure collagen, and this work will be repeated to see

whether or not slight traces of impurity might have been the cause of the reactions observed.

SUMMARY

The work briefly reported here would appear to indicate that the mechanism of absorption of catgut sutures consists first of hydration. This results in a slight swelling of the suture and a fairly rapid and significant loss of tensile strength during the early days after implantation. Then occurs a slow enzymatic digestion of the suture, the enzymes presumably coming from the polymorphonuclear leukocytes in the vicinity. As the suture disintegrates, the giant cells assist in removing debris and eventually only a small fibrous scar is seen.

The rate at which sutures are absorbed appears to vary from animal to animal, and presumably such would be the case in the human. Species differences are marked. The rat responds with a predominantly inflammatory type of cellular picture and rapid absorption. The dog, on the other hand, shows erratic but relatively slow absorption and the histologic picture is predominantly one of lymphocytosis and fibrosis.

Loss of tensile strength occurs more rapidly than the apparent disappearance of the suture. Thus, an appreciable loss of tensile strength can be observed, even though by microscopic examination no apparent disintegration of the suture has taken place.

Plain catgut induces more tissue reaction than does chromic catgut and, as might be expected, it is absorbed at a more rapid rate.

Factors such as an increase in body temperature and the presence of infection produce a more rapid absorption of sutures and a more rapid decline in tensile strength.

Although sensitization to catgut may occur, the high degree of purity of presently available materials would make it seem unlikely that such sensitization can be of clinical significance. In order to produce such sensitization in susceptible animals, reinforcement technics must be used and the reaction observed is purely a microscopic one; no gross abnormalities are observed in the sensitized animals.

SYMPATHECTOMY FOR OCCLUSIVE ARTERIAL DISEASE*†

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The medical profession, having gained control of most of the infectious and communicable diseases, and the complications of childbirth, has naturally turned to a fight against the degenerative diseases and their complications. Foremost among such conditions are the cardiovascular lesions. This is understandable, since the average age at which a person can be expected to die today is in the seventies, whereas fifty years ago the life span was only 47 years. This increased span of life has placed a large number of patients in our hands who demand therapy for complications of degenerative disease. If we can control these complications, we can keep these patients alive for a longer time and the possibilities of expanding the length of life become unlimited.

In the field of surgery we now find that 20 per cent of all the papers which appear in the various journals are written on the subject of the treatment of vascular lesions, thus showing the importance of, and interest in these so-far unconquered destroyers of life and limb. It still seems amazing that we can now open a heart and operate on it with visual accuracy, or insert a graft where a diseased artery no longer functions. These changes have occurred within a very few years and are due to advances in the field of anesthesiology, blood and fluid balance, antibiotics, anticoagulant drugs and experimental medicine and surgery.

SYMPATHECTOMY

My subject is one which has to do with an important part of our physiologic make-up, the sympathetic system and its effect on the vascular system. We have found that many of the diseases of the blood vessels are segmental and localized in nature. With arteriograms and aortograms we can now delineate these lesions, and often with direct surgical intervention we can remove the blocked area and replace it with a homologous or analogous graft of a vein type, or we can by-pass these defects with a graft. In other cases, it has been possible to remove a degenerated part of the artery with its thrombus, in about the same manner as one removes an arterial embolus in performing an embolectomy.

Much of this work is new. The technic of some of it has not been finally perfected, but we are all extremely interested in its future and accept the fact that in a very short time, and for the first time, something positive can be offered to the patient with an occlusive arterial or aortic lesion. In no way do I wish to

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detract from the fine work that is being performed to find the cause of the occlusive arterial lesion, and thus prevent it, either from a dietetic, an endocrine, or a developmental standpoint. My point is to show what we are trying to do surgically for these conditions.

There is a large group of patients whose arterial lesions are advanced, extensive or generalized. Such patients do not have an open distal vessel, so we cannot hope to replace the block by a graft. In other patients with aortic lesions grafts can be made if the local circulation can be improved beforehand. We believe that surgical sympathectomy will help these patients and that its effect often is like that of appendectomy in acute appendicitis. These patients who come to us for surgical care of their failing circulation have had every known type of medical therapy. They have had soaks and packs, they have performed their postural exercises religiously, and they have been on oscillating beds. They have had many kinds of vasodilators, placebos and sympathetic nerve blocking agents. When they reach the surgeon, they have exhausted all of the so-called conservative measures and come only because they, or their doctors, have realized that despite all the measures taken, no effective therapy has been found.

The sympathetic system is an extremely interesting one. It has a part to play in the symptomatology, prognosis and, we believe, the therapy of many lesions of the blood vessels. Some of these lesions are primarily sympathetic in origin, such as Raynaud's disease, causalgia, stages of frostbite, vasomotor dystrophy, and in some patients, the postphlebitic syndrome. These lesions can be helped directly by interruption of the sympathetic system in many instances.

There is still another group, however, in which the occlusive lesions are amenable to sympathetic surgery. In these patients, the vasoconstrictive effect manifests itself extensively and sometimes dominantly on a reflex basis, secondary to the stimulus of an occlusive arterial lesion. The occlusion itself may be precipitated or propagated by sympathetic overactivity.

It is my purpose to re-emphasize the part the sympathetic system may play in the course of occlusive arterial lesions and that sympathectomy as a treatment, judiciously applied, is an important, if not the most essential part of the therapy.

The surgeon's potential part in the therapy of occlusive arterial lesions is accepted by most, but not all of our medical confrères. This applies particularly to sympathectomy. Some are dubious about sympathectomy and deny that it has any value, believing that they can obtain better results without using that "last resort"—surgery. It is this term, "last resort," that has delayed the development of surgical therapy for these lesions. The surgeon often is called only when the lesion is hopelessly advanced. To overcome this feeling among the internists, we must show that the mortality and morbidity in these patients can be reduced by surgery, including sympathectomy.

THE SYMPATHETIC SYSTEM

The sympathetic system is still not well understood, although its anatomy and physiology have obviously been known for a long time. In the second century, Galen made reference to the sympathetic system, and Vesalius described

both the sympathetic chain and its ganglia in 1543. In the 16th century, Harvey discussed the connection between the circulation and the sympathetic system, and Claude Bernard in 1851, demonstrated that the sympathetic system controlled metabolism and body temperature. John Hunter first noted that the blood vessels contracted when subjected to trauma.

The sympathetic system appears to be primarily a defense mechanism in which a reflex vasoconstriction occurs in blood vessels in response to some stimulus, such as trauma. The trauma may be a direct one such as a bullet wound or a stab. Nature then attempts to prevent hemorrhage from the vessels by spasm. Blood is forced out from the injured and collateral vessels by this spasm so that they are not full of clots, and remain patent to carry blood again if their continuity is re-established. The trauma, to initiate this spasm, need not be an external one. An arterial plaque, clot or calcium deposit may release the same stimulus to reflex vasoconstriction.

The physiologic mechanism of this spasm as yet is not well understood. There is an autonomous spasm at the cell level. This was shown by Landis *et al.* (1) in the severed ears of a rabbit and repeated by Levinson and Essex (2) and Page (3). Page produced spasm in the vessels of a rabbit ear by injecting the substance contained in the blood of a shocked dog's ear. The chemical that causes this spasm has been given various names: Bach (4), Gopfert *et al.* (5) and Lewis (6) named it histamine; White and Smithwick (7) described it as sympathin; defibrinated blood was the term applied to it by Landis (8); and Page (3) and Chambers *et al.* (9) considered it some type of unknown toxin. To simplify the matter, our Clinic refers to this stimulator as "spastin."

Barnes and Trueta (10) and Phemister (11) demonstrated that there is also a nervous origin of vasoconstriction. It is not clear whether this is a direct neuropathway in which a reflex is set up by afferent stimuli from the source of the stimulus, to the cord and ganglia, and then by efferent stimuli to the vessels which go into spasm. It may be that the subsequent constriction is caused by a chemical which is injected into the blood by some reflex action. To determine whether this is of neurogenic or chemogenic origin is not of clinical significance. The important thing is to recognize the fact that spasm does occur in response to a stimulus. The degree of spasm varies with the stimulus and the individual response. In general, it depends upon the type and degree of stimulus, the condition of the blood vessels and sympathetic system, and the ability to respond to the stimulus.

In a patient who has occlusive arterial disease, the deposit of a plaque or clot upon a vessel wall may be sufficient trauma to initiate a spasm in the diseased vessel and its collateral vessels. If the spasm is great, it may of itself slow the blood stream and permit clotting. This possibility increases with the narrowed lumen and secondarily slowed blood stream.

Thus, one can see that occlusive arterial disease per se may be the initiator and propagator of a reflex vicious cycle which can become self-perpetuating. The interruption of such a cycle before final clotting occurs is of therapeutic value. It is obvious that the best place to interrupt such a mechanism is at the ganglion

itself. It has been demonstrated, to our satisfaction, that if this cycle is broken up before permanent damage has occurred, the progression to occlusion may be retarded, segmented, or may even be reversed.

THE ETIOLOGIC IMPORTANCE OF PERIPHERAL RESISTANCE

The role of peripheral resistance in the pathogenesis of occlusive arterial disease is of great importance and has not been emphasized sufficiently. For example, in a normal individual with a blood pressure of approximately 120/60 mm. of Hg, the fall in the systolic pressure from the aorta to the terminal branches of the arteries is about 25 millimeters of Hg—to 95 millimeters. When that blood reaches the capillary bed from the terminal arteries, the fall in pressure is 65 millimeters more, to a mere 32 millimeters. Therefore two and a half times as much pressure is required to overcome the resistance in the arteriolar bed as that necessary for the blood to pass from the heart to the end of the main arteries. Although the arterioles have a cross-section area only 25 times greater than that of the terminal artery branches, it takes 1,000 times more pressure to overcome the arteriolar resistance than it does to overcome that in the arterial branches. We believe that sympathectomy dilates the arterioles and reduces their resistance.

CONSERVATIVE TREATMENT

The conservative treatment of occlusive arterial disease is standardized, and in essence consists of:

1. *Keeping the skin covering or envelope intact.* Care must be taken to prevent any skin breaks due to poor hygiene, trauma, thermal changes, fungus infection or any other cause.

2. *Stimulation of collateral circulation and dilatation of vessels in the original circulation, medically, in the form of warm baths and postural changes.* Making use of the affected part, below the point of fatigue, requires small amounts of blood. This use tends to keep the arteries and collateral vessels functioning, and favors the development of additional circulation.

3. *Avoidance of all constricting or spastic elements, whether they be physical or chemical.* Tight-fitting garments, bandages or shoes must be avoided, and care must be taken especially that casts or dressings do not restrict the circulation. The main chemical to be avoided is nicotine, in the form of tobacco. There is no longer doubt of the detrimental effects of nicotine on the circulation. Other chemicals to be avoided are the vasoconstrictors, including those of the ergot family.

4. *Anticoagulants.* As the blood stream slows down with the accumulation of occlusive elements in the arteries, there is an added tendency to thrombosis. Anticoagulants, used correctly, will prevent clotting in the slowed stream (such as occurs in arteriosclerosis) for a longer time than in patients who do not have such anticoagulants in their blood.

SURGICAL TREATMENT

Efforts at surgical treatment have been made in two directions. Since blocks of an artery are frequently segmental, it is often possible to bridge or by-pass such

blocks with grafts. For such an operation, a distal open vessel is necessary. This therapy is in the process of perfection and has great potential value.

The other direction of surgical effort is toward the release of vasoconstriction, and this is accomplished by interrupting the sympathetic fibers causing the constriction.

Collateral circulation

In a case of segmental occlusion the patient must depend upon one of three types of collateral circulation, or some substitute for the main vessel, if the part is to survive. The collateral circulation can be subdivided into:

1. *Hypervascularization vessels.* These vessels are small. They may be preformed, or may dilate or develop after the occlusion occurs.

2. *Supplementary branches.* These vessels are hypertrophied small branch arteries in the muscles and around the joints. They are partially effective in maintaining the circulation.

3. *Bridging collaterals.* Our Clinic calls these "vital detours." Such vessels are larger, and may attain sufficient size to permit complete function of an artery distal to the block.

All three types of collateral circulation are improved by surgical sympathectomy.

Anatomy of the lumbar sympathetic system

The anatomy of the lumbar sympathetics has been traced by many observers, but more recently by Edwards (12), Ray (13), Kuntz (14), and ourselves (15). This system primarily is a plexus and *not* a nerve. The lumbar chain begins as a thin, string-like attachment to the twelfth thoracic ganglion. The sympathetic chain usually is lateral to the vertebra, but tightly attached to it, and often is crossed over by the lumbar veins at right angles. The ganglia vary in number and may fuse. Normally, they are three or four in number, but there may be as many as eight. Any thickening in the cord itself may be a ganglion. Each lumbar nerve has from one to three or four communicating branches, and they may anastomose widely with each other. They may arise at the level of the ganglia, but also may arise *between* the ganglia. In general, the twelfth, first and second lumbar rami ascend after their origin; the third usually runs transversely, but it may ascend or descend; and the fourth and fifth usually descend in their course. Some of these rami will run in the psoas muscle itself. The external iliac and genito-femoral nerves also serve at times as carriers for sympathetic fibers and in such cases may account for the failure to accomplish adequate denervation when only the chain itself is removed.

The fourth lumbar spine anatomically is at the level of the iliac crest in the male; however, in the female the fourth disc or fifth lumbar vertebra is at the level of the crest. In the usual position used in retroperitoneal sympathectomy, the promontory of the sacrum is elevated above the crest. Lumbar veins, periaortic lymph nodes, and their nerves and blood vessels confuse the operative picture. An extra muscle origin of the crux of the diaphragm from the vertebrae

may cover the chain, as may other fascias and muscles in this area. Identification of the sympathetics may be further obscured or confused by other nerves, blood vessels, lymph nodes, lumbar veins, and even the ureter.

Technic of sympathectomy

In our experience, adequate sympathectomy cannot be obtained by removal only of the second and third ganglia, as is advocated in most operative technics. Lumbar sympathectomy, to be complete, should always include every lumbar ganglion, including the fifth lumbar if it exists, often the twelfth dorsal, and each nerve filament that makes up the plexus. Poor, or equivocal results reported by many clinics after sympathectomy are due, we feel, to entirely inadequate effacement of the sympathetic innervation. This opinion is further emphasized by the fact that we have re-operated on, and have successfully removed ganglia from 16 patients in our series who had had previously a so-called sympathectomy with poor results.

Anesthesia

Lumbar sympathectomy in our hands is most safely performed under *spinal anesthesia*. We are certain that many of our older patients, subjected to sympathectomy safely, could not have withstood a general anesthetic. Collins (16), of our Anesthesiology Department, keeps the anesthesia level ideally low with a hypobaric technic, but whether a hyper- or hypobaric technic is used depends on the experience of the anesthesiologist.

We feel strongly that spinal anesthesia should *not* be augmented by Pentothal or other general anesthetics. These agents are too often given for the benefit of the anesthesiologist and not for the benefit of the patient. In a series of 30 operations on patients over the age of 80, spinal anesthesia has proved to be safe. Only 1 death occurred in this group.

RESULTS OF SYMPATHECTOMY

During a six-year period, from July 1948 to July 1954, we have performed 396 surgical sympathectomies on 368 patients. Of these operations 338 (70 per cent) were performed on 250 patients for occlusive arterial disease.

These latter operations were performed on 258 males and 75 females—a ratio of 3 males to 1 female, which corresponds to the sex incidence of this disease. The average age of these patients was 58, the oldest being 87 and the youngest 17. Thirty sympathectomies were performed for occlusive arterial disease on patients over 80 years of age.

A critical analysis has been made of these patients' operative response. The patient is interested in two things only: will he lose his life, or his limb, from the operation? There can be many extenuating circumstances contributing to these lamentable end-results. Extensive and rapidly progressing disease, advanced age, severe cardiac, renal or diabetic complications, the continuation of smoking, further trauma, and sepsis or gangrene already present at the time of sympathectomy, all may play an important part in the result. If the surgeon desires, these

blocks with grafts. For such an operation, a distal open vessel is necessary. This therapy is in the process of perfection and has great potential value.

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factors may be applied to his results, in order to prove a point. For example, in some of our patients sympathectomy was performed in an effort to amputate at a lower level than would otherwise have been possible.

We have followed our patients postoperatively for from six months to five years. Since death, or the loss of a limb usually occurs shortly after operation if the procedure fails, we consider our findings representative.

Deaths after sympathectomy

Of the 368 patients, 11 (3 per cent) died. Nine of the 11 were over 60 years of age and one was over 80. Six of these died of coronary occlusion, 1 of progressive gangrene, 3 of generalized arteriosclerosis and 1 of mesenteric thrombosis. The operation per se did not appear to contribute to their demise, but since they died during the postoperative period or shortly thereafter, they are included as operative deaths.

Amputation after sympathectomy

Two hundred and three of the patients had arteriosclerosis without diabetes. There were 22 amputations in this group, or an amputation rate of 10.8 per cent.

Diabetes complicated the arteriosclerosis in 101 patients and 31 amputations were required in this group—a rate of 33 per cent. This figure shows the role that infection, so frequent in the diabetic, plays in determining the outcome.

There were 4 amputations after the 20 sympathectomies performed on patients with thromboangiitis obliterans. Thus there was a 20 per cent amputation rate in this group.

In discussing extenuating circumstances, we should like to point out that only the most advanced cases of Buerger syndrome were operated on. Our overall picture of 4 amputations for thromboangiitis obliterans during the six-year period, however, speaks well for conservative management in this group.

Among the 9 patients who had acute arterial occlusions and underwent sympathectomy, there were 2 amputations—a rate of 22 per cent.

We had, therefore, a total amputation rate of 19 per cent—64 amputations after 338 sympathectomies. Of these amputations, 28 were below the knee, and 36 were above the knee. It is our opinion that sympathectomy definitely enabled us to choose lower operative sites in the 44 per cent of patients who had amputations below the knee.

Relation between presenting symptoms and amputation rate after sympathectomy

We appraised the presenting symptoms of these patients in relation to the amputation rate. The largest number of our patients (198) were operated on for coldness and claudication of an advanced type. Only 8 (less than 4 per cent) of those required amputation of the leg. When there was ulceration and infection (67 patients), 32 per cent (22 patients) required amputation. When there was actual gangrene (38 patients) 67 per cent (25 patients) required amputation. It is significant that of the 18 patients who had pain at rest, 7 lost their limbs. Thus, when there was gangrene or ulceration and infection (105 patients), 44

per cent lost a limb but 56 per cent did not. Gangrene, pain at rest and ulceration were the most serious symptoms prognostically, and in this series they occurred in that order.

CONCLUSIONS

On the basis of the foregoing data, and judging our results critically, it is our opinion that sympathectomy is an excellent ancillary therapeutic measure for use in patients with occlusive arterial disease, provided that, 1) gangrene is not already present, 2) the operation is not used to replace the fundamental medical management, 3) the patient has a fair chance of surviving the operation, 4) the patient has given evidence of a desire and ability to stop smoking, and 5) all other corrective measures for the underlying disease are continued.

The operation is not lethal, even in the geriatric age group, and the death rate parallels closely that of the disease itself without operation.

In our series of patients with advanced occlusion, it has been demonstrated that in 274 out of 338 sympathectomies there was no need for amputation following sympathetic denervation.

It should be emphasized that sympathetic denervation must be a complete effacement and not a mere partial resection, and it is our feeling that many poor results are due to an ineffective or inadequate sympathectomy.

Sympathectomy is not a cure-all but, when carefully employed, may be a means of maintaining the delicate balance between the vascular supply, infection and loss of limb.

Pain at rest is a dangerous symptom. In patients with active gangrene, amputation of the limb will follow two out of three times in spite of, and not because of sympathectomy. If gangrene occurs after sympathectomy, it is because the disease was already irreversible or because operative trauma caused an occlusion.

When the symptoms are those of claudication and coldness, 95 per cent of patients will not require amputation of the limb after sympathectomy. When open lesions are present, 2 patients out of 3 will not require amputation. Even when gangrene is present, 5 or 6 of every 10 patients will not lose a limb after sympathectomy. Admittedly, the disease is progressive, and some patients may require amputation later. Sympathectomy, however, appears to be a safe, frequently successful treatment for occlusive arterial disorders, and aids in retarding the progress of the disease.

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SUCCESSFUL NONSURGICAL REPERITONIZATION OF THE PELVIC FLOOR FOLLOWING RADICAL EXCISION FOR CANCER OF THE RECTUM*

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Too frequently radicality in surgery for cancer of the rectum is restricted by overly cautious and usually groundless practices in technique. In the pursuit of ever greater five-year survivals and salvage rates our experience has been that operative morbidity and mortality vary but little, despite the transgression of most customary conventionalities. To mention a few: Sudek's point of viability for blood supply is now disregarded and we ligate with impunity the inferior mesenteric artery at its origin in order to permit a clean dissection of the inferior mesenteric regional lymphatic zone. We ligate both internal iliac arteries to aid hemostasis, and we successfully transplant ureters and remove pelvic organs with their blood supply and lymphatic drainage systems. In this paper I should like to discuss the removal of wide areas of peritoneum and the relative safety of permitting these exposed surfaces to remain deperitonized.

PRELIMINARY OBSERVATIONS

Prior to developing the technique to be described we felt that the simple procedure of leaving bare deperitonized surfaces would offer little hazard of adhesions or infection. To substantiate this impression we removed the entire parietal peritoneum in 20 laboratory dogs (1). No deaths occurred and there were no instances of intestinal obstruction. In 10 of the dogs, open end-to-end colic anastomoses were performed without previous bowel preparation. No increase in morbidity occurred and infection was minimal or absent. These dogs were all subjected to follow-up laparotomies and microscopic studies of the reperitonized surfaces. In each, a glistening surface resembling the original peritoneum was noted. Adhesions were no more numerous than if the peritoneum had not been removed. Repair processes were evident within a few days, and at the end of six weeks there was a re-formed surface, microscopically as thick as the original peritoneum.

With the realization that these bare surfaces offered no particular risk to removing peritoneum we sought to determine what risk might be associated with leaving the pelvis and peritoneal cavity open from below. The results observed in 588 patients undergoing the "pull-through" operation without reconstruction of the pelvic floor furnished valuable information. Complications such as adhesions or intestinal obstruction in these patients were remarkably low, despite the fact that in many of them small intestine had found its way down into the low pelvis alongside the transplanted colon.

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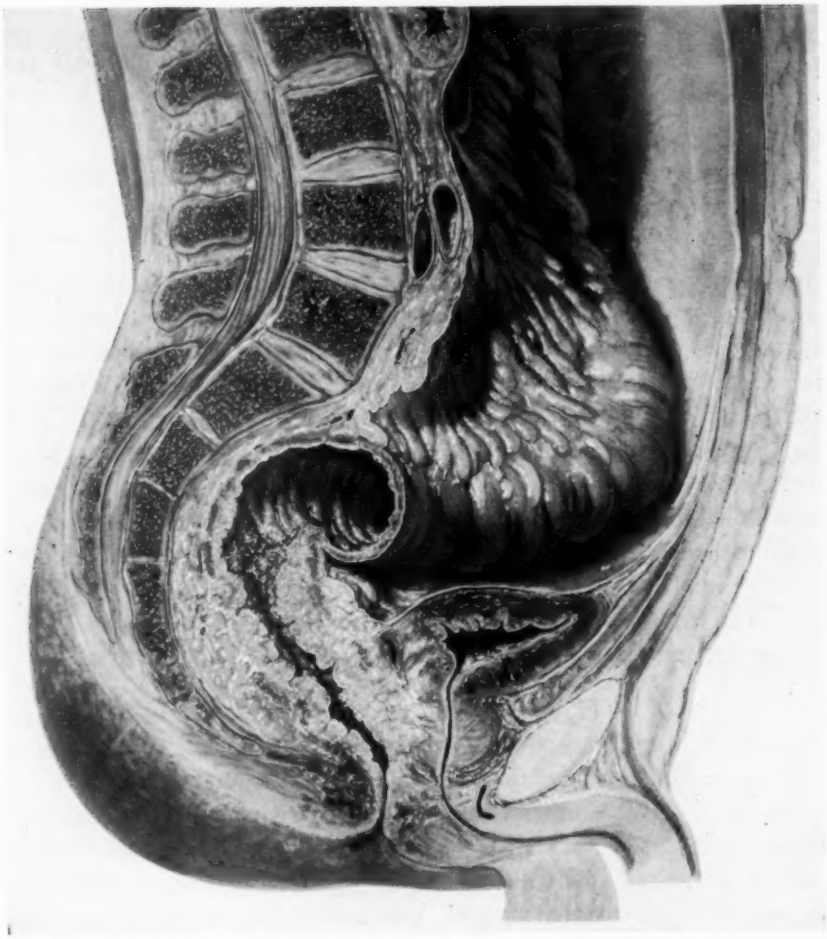

FIG. 1. Note extensive local spread of cancer, with involvement of peritoneum and pelvic viscera. Such patients may often be salvaged by adequate surgery and wide removal of peritoneum (Reproduced with permission of the publisher, from Trimpi, H. D. and Bacon, H. E. (reference 1).).

REPERITONIZATION FOLLOWING PELVIC EXENTERATION

Next the procedure of leaving open the pelvic cavity was put into actual practice. Among the first patients selected were those in whom cancer had become widespread through local extensions and dissemination (Fig. 1). Total pelvic viscerectomies were performed with transplantation of ureters to the skin or bowel. Due to wide removal of the peritoneum, no attempt was made to repair the pelvic floors. Instead, from below, a large sheet of rubber dam was inserted and packed with 2-inch vaginal gauze (Fig. 2). At first these packs were left in situ from ten to fifteen days. Upon removing them, we were pleased to find a complete walling-off of the abdominal cavity from the true pelvis. No protrusion of small intestine occurred and there were no instances of intestinal obstruction.

As our experience increased we began removal of the packs as early as the eighth postoperative day, in order to give the patient more comfort and ease in

FIG. 2. Illustrating the method of packing an exenterated pelvis by means of a rubber dam filled with two-inch vaginal gauze packing. No attempt has been made to reconstruct a pelvic floor. Regeneration is so complete that within ten days the pack can be safely removed without danger of herniation of small bowel. Adhesions are minimal. (Reproduced with permission of the publisher, from Trimpi, H. D. and Bacon, H. E. (reference 1).).

ambulation. Among 42 patients (derived from our total series of 1,495 cases) in whom such Mikulicz-type packs were inserted there were only 2 in whom the packs had to be replaced after eight days. In both of these patients, small intestine had found its way into the low pelvis. It was a simple matter to replace the packs and leave them another four days, at which time they were removed and no further herniation was evident.

In 1 patient an unexpected complication developed, which deserves some comment. In this individual, a woman of 62 years, a carcinoma was discovered which involved the mid-rectum and extended to the vagina and subperitoneal tissues. In the absence of demonstrable distant metastases, and with the hope of cure, a radical procedure was deemed the operation of choice. Consequently, a posterior viscerectomy with excision of rectum, sigmoid, vagina, uterus and adnexa, asso-

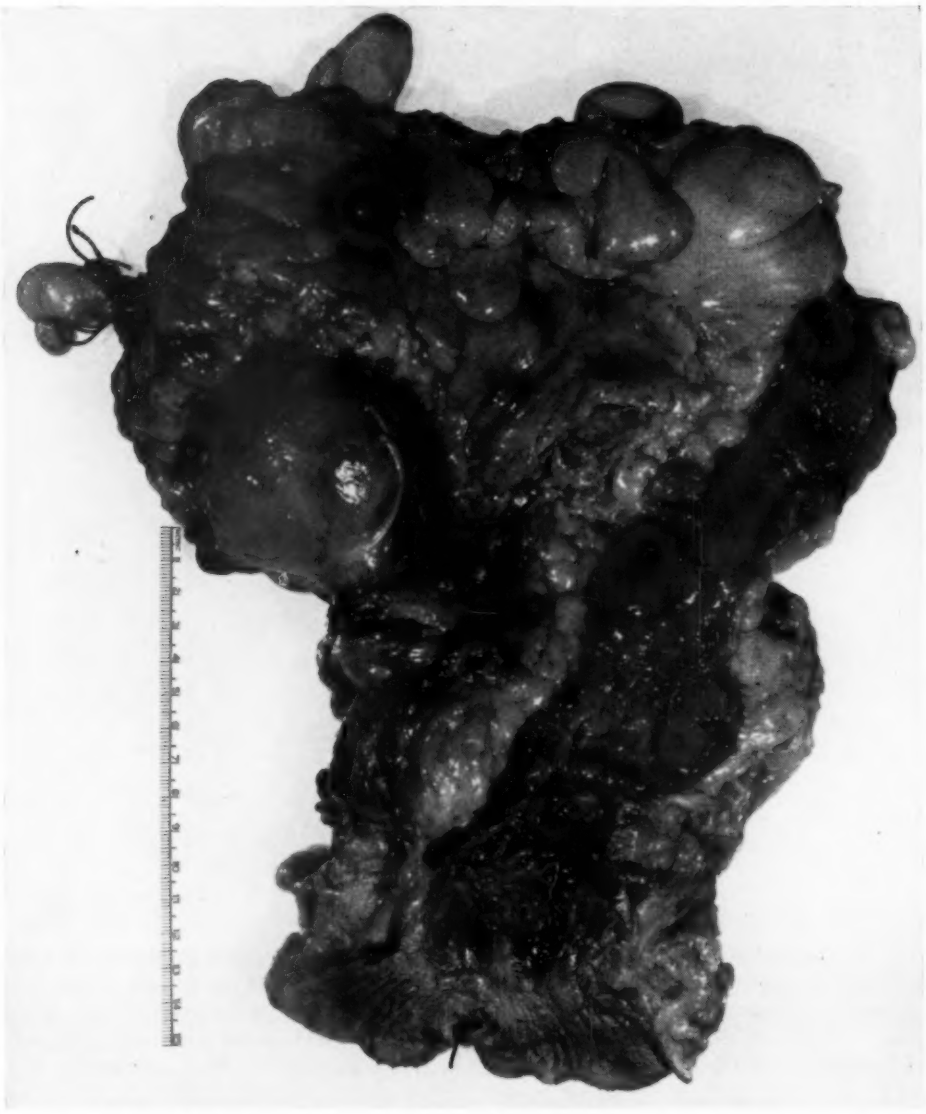

FIG. 3. Cancer of rectum with invasion of cul-de-sac, vagina and cervix. Posterior viscerectomy performed without closure of pelvic floor (Reproduced with permission of the publisher, from Trimpi, H. D. and Bacon, H. E. (reference 1).).

ciated lymphatics and blood vessels was carried out (Fig. 3). Large denuded peritoneal surfaces resulted and the pelvic floor was not reconstructed. Following the perineal phase, the usual rubber dam was inserted and packed with 2-inch vaginal gauze. In order to achieve greater hemostasis from the denuded pelvic cavity and vascular beds, considerable pressure was employed in packing. As a result, some days after removal of the pack, urine was noted in the wound; the source was discovered to be in the right lateral pelvic wall. A later exploratory laparotomy revealed pressure necrosis of the right ureter for several inches. It

had been crushed against the lateral pelvic wall. Treatment consisted in nephrectomy and ureterectomy on the right (after finding the function of the left kidney and ureter to be satisfactory). Such pressure is unnecessary, as the pack will remain in place for many days without being extruded. If pressure is needed for hemostasis, it should be relieved within twenty-four hours, and a less forceful pack inserted to close the pelvic outlet.

OPERATIVE TECHNIC

The abdomen is opened through an extended left paramedian incision, the rectus muscles being retracted laterally. After palpation of the liver, to determine whether or not gross metastases are present, the large bowel and pelvis are inspected. The extent of the operative procedure is now determined. Let us say that the lesion involves the rectum up to the peritoneal reflection; it is fixed and has extended to the vagina and cul de sac. The procedure of choice is posterior viscerectomy with sacrifice of the pelvic peritoneum and removal en bloc of the internal genital organs as well as the vagina.

Prior to manipulation of diseased tissues the upward blood flow is interrupted to prevent the dislodging of tumor cells within the portal system. An incision is made at the base of the mesosigmoid overlying the aorta. This is carried upward to the origin of the inferior mesenteric artery. The duodenum is carefully retracted upward. Dissection exposes the inferior mesenteric vessels and these are clamped, divided and ligated. The sigmoid colon is now liberated from its secondary pelvic peritoneal attachments. Dissection reveals the left ureter and ovarian vessels. The ovarian vessels are divided. An incision is carried laterally, dividing the peritoneum of the left pelvic wall, parallel and below the level of the external iliac vessels. The distal peritoneum with the suspensory ligament of the ovary, and broad ligament are retracted medially. The round ligament is divided. Now the left pelvic wall may be bared of peritoneum and adnexa, from the promontory laterally to the bladder. Blunt dissection continues downward, with exposure of the hypogastric vessels and their branches. The uterine artery and the left middle hemorrhoidal artery are divided at their origins. Blunt dissection frees the rectum from its posterior attachments.

On the right side the dissection is carried downward in a manner similar to that on the left. It begins at the previous incision made over the aorta and continues laterally, just below and parallel to the external iliac vessels. The right ureter and ovarian vessels are exposed. The ovarian vessels are ligated and the adnexa freed and retracted medially. Hypogastric vessels and tributaries are exposed.

The question arises whether or not to ligate the hypogastric (internal iliac) arteries. Usually much less bleeding results if this is done. Before ligating, however, one should be certain that there are femoral pulsations and external iliac pulsations on both sides. In a recent case, ischemia of the right leg developed because we had not discovered an arteriosclerotic plaque obstructing the right femoral artery. The patient had been depending on his right internal iliac artery for much of the collateral supply to his right leg. If ligation of the vessels is elected, they are best ligated in continuity with chromic catgut.

With ligation of both middle hemorrhoidal and uterine arteries, the uterus is now freed from the bladder and the dissection is carried downward, separating the bladder from the vagina. Vagina and rectum are separated from their lateral attachments. No attempt is made to manipulate the growth or separate its attachments to rectum, vagina, or uterus. These organs have been mobilized down to tip of coccyx and may be removed from below without disturbing cancerous tissues.

The descending colon is next mobilized and brought medially into the wound where a site for permanent colostomy is elected. The mesocolon is divided laterally, from the previously divided inferior mesenteric vessels out to the bowel. Inferiorly the aorta and vena cava are stripped of their mesocolic attachments and lymphatics. The bifurcation of the aorta and presacral tissues are widely cleared of all lymphatics.

The descending colon is divided and its proximal part brought out through a stab wound or through the operative incision as a permanent colostomy. The abdominal wound is repaired, using interrupted figure "8" sutures of #30 alloy steel wire in the fascia and peritoneum. Alloy steel #35 is employed in the subcutaneous tissues and skin.

The perineal phase is performed with the patient in lithotomy and modified Trendelenburg position. The anus is closed with stout silk and semicircular incisions are begun at the mid-portion of each labium and carried posteriorly to meet each other at the tip of the coccyx. Posteriorly, the incision is deepened and is carried deep in front of the coccyx, where Waldeyer's fascia is divided and the pelvic cavity entered. The dissection from above is encountered. By inserting one finger above the right levator muscle, its attachments to the pelvic wall are palpated and divided. This incision is carried outward through fascia and ischiorectal fat in such a way that the gluteal muscles are exposed. The same procedure is carried out on the left. By reaching into the pelvis at this point, the liberated bowel may be delivered along with carcinoma, uterus, adnexa, and associated peritoneum. The only attachments left are those anteriorly, where the low vagina is still attached to the bladder and triangular ligament. These are divided by deepening a transverse incision made from the mid-portion of each labium, inward and proximal to the urethral meatus. The vagina is now dissected upward until the previous dissection from above is reached. The whole specimen can now be delivered en bloc.

The large pelvic cavity is inspected for bleeding and hemostasis is assured. A square of rubber dam two feet wide is selected and placed in the pelvis. As it is introduced upward, any small bowel that may have found its way into the pelvic outlet is displaced upward until the promontory of the sacrum is reached. The rubber-dam square is now packed from below with 2-inch vaginal gauze.

After eight days, the pelvic pack is removed. Its presence does not preclude early ambulation. Contamination by urine despite an adequate urethral catheter may sometimes give rise to local infection, but this is seldom important and we have not observed abscesses in the walled-off areas. The rubber dam acts as an excellent drain and serous fluids do not accumulate in the low pelvis. The dam can be removed without risk of its being adherent to the newly developed pelvic floor.

Inspection within the wound reveals a definite layer of tissue walling off the abdominal cavity from the pelvis. Small bowel may be outlined through this wall but its herniation downward is unusual. Obstruction, abscesses, and complications within the abdominal cavity have not occurred. Second-look operations on 6 of these patients revealed no more adhesions than would be found after a standard Miles operation with closure of the pelvic floor.

COMMENT

A procedure is outlined for the treatment of cancer of the rectum, which meets the requirements of good cancer surgery:

1. Ligation of the venous drainage system prior to manipulation, and prior to disturbing the cancerous mass.
2. En-bloc excision of the involved tissues, without dividing cancerous structures.
3. Wide removal of lymphatics, with especial attention to eradication of primary and secondary lymph nodes.
4. Restoration of function and rehabilitation, without sacrificing radicality of operation or increasing morbidity and mortality.

No attempt is made to reconstruct the pelvic floor. This allows wider removal of the peritoneum, without the constant need of preserving tissues to close the pelvic outlet. It eliminates the necessity of stripping peritoneum from the bladder

or of utilizing small intestine to cover the open area. The danger of a split in a taut repaired floor is eliminated. There are no small perforations through which small intestine may become strangulated. The hazard of displacing bladder, ureters, or other organs is reduced, and foreign-body reactions, such as may follow repair with chromic catgut, are avoided.

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ULTRASOUND WAVES IN THERAPEUTICS: A REVIEW OF THE PRESENT STATUS*

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"Target action," as a descriptive phrase, is becoming well established and much discussed in the field of therapeutics. The newness of this concept is seasoned considerably by one of the phases encompassed, namely, synergistic action. The currently recognized interactions and interdependence among the endocrine system, the vegetative nervous system, and the vitamin balance fall within this sphere.

Ultrasound energy, confined to the treatment of abnormalities, lends itself well to the concept of target action. This viewpoint directs reasoning into clear channels and avoids confusion. Such a perspective is vital to one who is just entering the investigative field and who will be confronted with an avalanche of comparatively recent literature on the subject.

FUNDAMENTALS OF THERAPEUTIC ULTRASONICS

Ultrasonics, as applied to therapy, is a special form of acoustical energy, produced and delivered from a transducer or soundhead and applied to an area to be treated.

Ultrasound waves differ from ordinary sound waves in that they are delivered at high frequency, which is generated at near 1 megacycle. Their characteristics differ from those of conventional sound waves. The perceptive capacity of the human ear cuts out at 18,000 to 20,000 vibrations per minute. The term "ultrasonic" refers to the higher inaudible frequency ranges.

The high-frequency oscillations in most of the units now in use are produced by generating a high frequency electrical field and leading it through a coaxial cable to a mobile transducer or soundhead, within which is anchored a specially designed quartz crystal. The piezoelectric response of the quartz emits high oscillatory impulses to the exterior of the soundhead and it, in turn, sends them to the area to be treated. Both air and vacuum provide a barrier to these waves. However, if the mass contacted is homogeneous, the rays will penetrate unobstructed. A contact known as a coupling, between the skin and the soundhead is, therefore, essential. Water or a lipoid is normally used for the coupling (Fig. 1).

To the therapist first contemplating the use of ultrasonic energy, a few vital points should be thoroughly understood:

1. The construction of the soundhead is important, for here is the "heart" of the energy.

2. The size and shape of the soundhead are important. The size of the quartz

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crystal governs the total emitting field—the bundling effect, with the differential between the central and peripheral energy beam in respect to the circumference. Still more important is the dosage received by the patient in contrast to the dosage indicated on the dial of the unit.

3. Is the energy continuous or pulsed? If pulsed so that there are cooling effects, then the ratio between the duty and rest cycles is important.

These three factors have led to much adverse discussion, rather than to confusion relative to ultrasonic energy itself.

Heretofore the physical energies used in therapeutics belonged in one of four categories: heat, radiation, electrophoresis, or mass movement. From this standpoint, ultrasound energy is a new agent, and therapeutically it has considerable potential. Its actual technical application is not difficult and can be learned rapidly by qualified technicians. Frequencies of near 1,000 kilocycles, and dosages of not more than 4 watts per square centimeter, are becoming universally accepted.

ULTRASOUND WAVES IN DIAGNOSIS

In scientific laboratories, extensive studies have been in progress for several years, but the clinical applications of ultrasound waves have only recently been

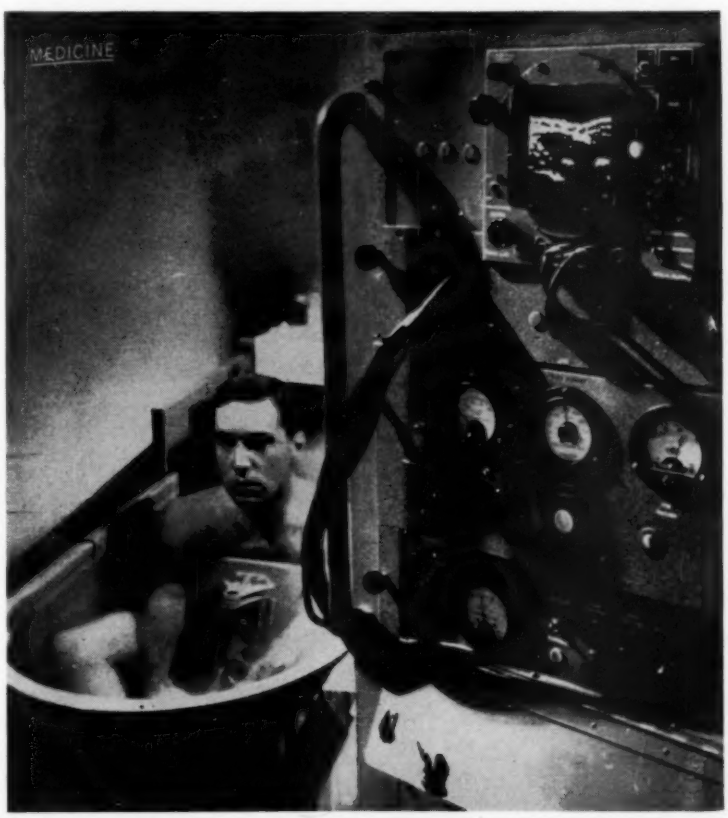

FIG. 1. Illustrating ultrasonic unit used in diagnosis. Note subject immersed in water (coupling) and screen at top of unit. (Courtesy, Howry, D. B. (13, 14) and *Life* **37**: 71 (Sept. 20) 1954.)

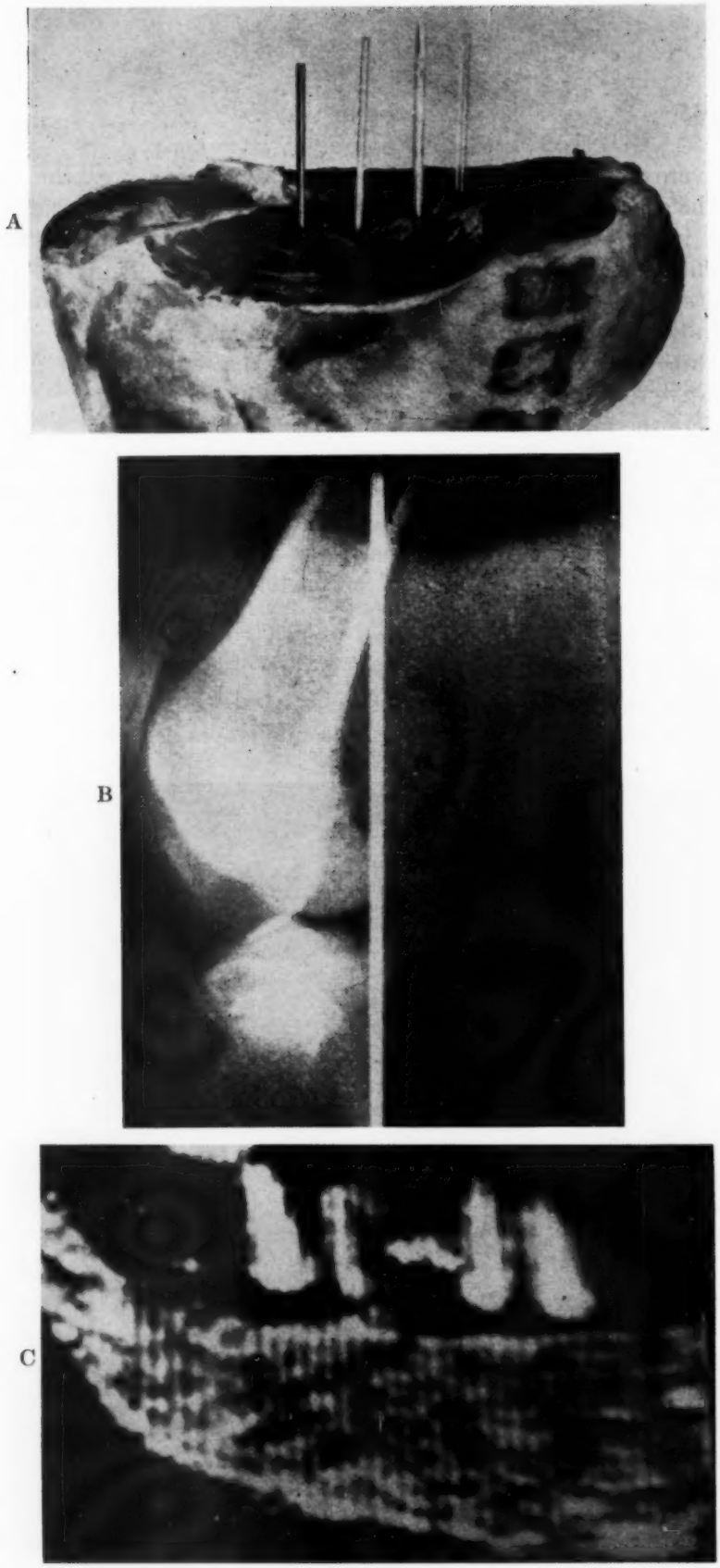

FIG. 2

A. Mutton leg containing spikes of brass, wood, plastic and glass. All are seen.

B. Same tissue as in A, after exposure to x-rays. Note that only the brass spike and the bone are seen.

C. Same tissue as in A, under ultrasonic exposure. Note that all spikes can be seen.

(Courtesy, Howry, D. B. (13, 14) and *Life* **37**: 72 (Sept. 20) 1954.)

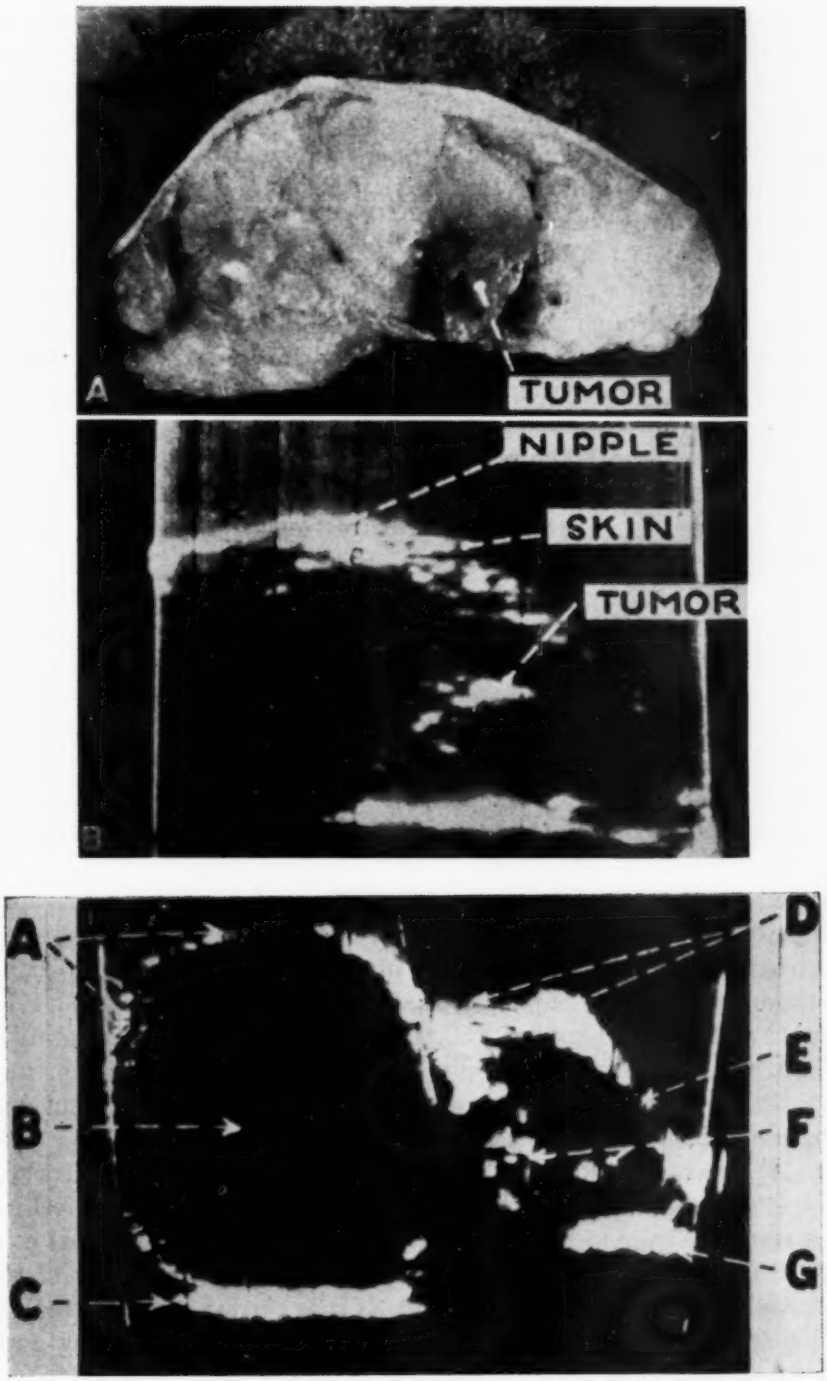

FIG. 3. Illustrating differentiation of soft tissues by ultrasound waves. (Courtesy, Howdry *et al.* (14).)

Above: Section of breast, with tumor. A—Gross appearance. B—Under ultrasonic exposure.

Below: Cyst of the kidney. A, C, D, G—Kidney borders. B—Cyst. E—Arteriole. F—Calyces.

delineated. In Europe, Pohlman (1, 2), Buchtala (3) and Tschannen (4, 5), and in America, Heuter and Bolt (6), Dussik (7), Zach (8), Schwan and Carstensen (9) and Schwan, Carstensen and Li (10) have contributed voluminous studies indicating the potential value of ultrasonics in clinical diagnosis. The possibilities of ultrasound energy in diagnosis must be comprehended by the therapist (11).

The fundamental principle of ultrasonics in diagnosis is that part of the high-frequency sound waves passing through the body are reflected and produce an echo at tissue interfaces such as the junction between fat and muscle. Their behavior differs, depending upon the density of the tissue involved. The echoes are recaptured and led through amplifiers to the cathode-ray tube of an oscilloscope, where they produce a spot, or rows of spots, thus forming a picture visible on a screen, somewhat like television (Fig. 1). The behavior of ultrasonic waves at tissue interfaces is most important to the therapist (12).

Figure 2 (13, 14) reveals the potential advantages that ultrasonics may have over roentgenography. Additional figures in the reports of Howry (13) and of Howry, Stott and Bliss (14) brilliantly illustrate cysts, malignant growths, and other structures revealed by the process (Fig. 3).

CLINICAL APPLICATION

War is humanity's curse, yet scientific development for the good of humanity is frequently the by-product of research initiated for the purpose of death and destruction. Thus the minute "sonar pip," vital in locating enemy craft, is now transferred to the realm of management of disease. Clinical research has established a place in therapeutics for this new physical agent. My objective is to bring together the extremes of doubt and dogmatism that are the cause of most of the current divergent discussions.

The therapeutic application of an agent will flounder without a knowledge of the biologic principles involved. The use of ultrasonic energy is no exception. Biologic reactions to it are the subject of extensive investigations.

That thermogenesis plays a part in its effect is accepted (12, 15–17). Some investigators venture to call application of the waves "ultrasonic diathermy" (10). Others with equally authoritative opinions relegate the thermal factor to a secondary position and project as the primary factor a combination of mechanical, physiologic, and intracellular metabolic chain reactions.

Bauer (18), recently called upon to state the present position of ultrasonics in therapy, very aptly cautioned that unless one kept his scientific feet on the ground it would be easy to conclude that the thermal and nonthermal concepts had divided ultrasonic therapeutics into two camps—east and west of the Atlantic Ocean. This viewpoint is significant. If it is carried beyond research into actual clinical practice, it will lead to controversy, misunderstanding and confusion, for no logical reason.

Certainly heat is produced, just as when any energy is liberated within or driven into tissues, but the tissue heat is not palpable as in diathermy. It must be determined by sensitive instruments such as thermocouples. Therefore, heat must be assumed but not to the extent that the therapist need fear burns, as with other

physical agents. Instead, he must recognize the "power" that ultrasonic waves possess.

The group of clinicians recognizing the thermal effect, but emphasizing the nonthermal phase, is well represented (3, 19). Both Zach (8) and Tschannen (4) have noted undeniable evidence of the action of ultrasound waves upon the vegetative nervous system. VanWent of Amsterdam, in her book now translated into English (20), reviews in detail all ramifications of the subject. In America, clinicians continuously report results that indicate the therapeutic value of ultrasonic energy (21–29).

The essential points for the therapist are: 1) a clear concept of the basic physics, 2) the proper comprehension of dosage, which involves engineering of the unit itself and the technic of application (30), 3) the biologic effects of ultrasound waves, and 4) the selection of conditions responsive to treatment.

INDICATIONS

Many indications for ultrasonic therapy have been established. Others are under study. The question will be asked whether it is specific for any malady. It probably is not, except for selective tissue heating at the interfaces. When beaming and deep penetration without excessive heating are desired, it is the physical agent of choice.

Some refer to the energy as a decongestive agent. In acute sprains and bruising injuries, as well as in acute bursitis, its use gives rapid relief of symptoms. It is not unusual to see an acute hematoma rapidly disappear. Myalgias, especially low back pain, myositis, neuralgias, and arthralgias, have been treated with results superior to those obtained with other physical agents. Table 1 lists the diseases treated up until 1952. Since then, over 1,000 patients in addition have received this therapy.

Most of the conditions cited require treatment locally at the site of involvement. When the various biologic reactions to ultrasound waves are considered, such as their effect on intracellular metabolism and their action on the vegetative nervous system, a host of other indications becomes apparent.

VanWent (20) reports enlightening experimental and clinical studies on displaced nucleus pulposus. Bierman (28) has studied the effect of the energy on fibrous tissue and Dupuytren's contracture. Stuhlfauth (19), Tschannen (4), and Zach (8) report on neural pathways and peripheral vascular disease. These are but a few of the many clinical reports (31, 32) from all parts of the world.

Aldes and Jadeson (33), reporting on the value of the use of ultrasound waves in geriatrics, confined most of their studies to the joints. Behrend and Weiss (23) present a broader discussion of the use of ultrasonics in the aged. In my experience, it has not been unusual to observe a more clear-cut systemic effect in elderly individuals as compared with those in younger age groups.

Geriatrics is vitally concerned with the cardiovascular system and its relationship to pain, trauma and shock. In this connection, mechanical dentistry assumes importance as an indication for ultrasonic therapy. Osserman (34) is conducting research in this field. Figure 4 shows an ultrasonic dental handpiece,

TABLE 1

*Constructed to Present Summary Picture of Several Diseases Treated with Ultrasonic Energy**

Clinical Group	Total Cases	Sex	Age—Range in years	Duration of Complaint	Previous Therapy	Results: None	Moderate	Good
Autonomic Nervous System								
Bronchial Asthma	3	F—3	17 to 50	8 to 20 years	Conventional, all failures including ACTH, etc.	1	1	1
Circulation Disorders, Legs—Skin—Ulcers	10	M—4 F—6	61 to 86	6 mos.–5 yrs.	None—Routine—Some surgical	2	4	4
Gangrene Toes	5	M—2 F-3	39 to 62	3 wks.–1 yr.	Conventional, all failures	1	1	1
Bones and Joints								
Acute Trauma: Joints, Back and Fractured Ribs	72	M—52 F—20	17 to 46	2 hrs.–2 wks.	None, to usual first aid	8	12	52
Radiculitis	10	M-6 F—4	27 to 42	2 mos.–6 mos.	Various, including ACTH	4	3	3
Arthritis: Rheumatoid, Osteo, and Mixed Types	130	M—38 F—92	41 to 78 Aver. 55	5 to 40 years	92% Failures with modern therapy including Cortisone, ACTH and B-12	77	38	15
Disc Syndrome	0					0	0	0
Disc Syndrome, Van Went, Amsterdam, Holland	34	M—10 F—24	18 to 61	Not reported	Not reported	2	—	32
Pain and Distress Syndromes								
Acute Bursitis	10	M—9 F—1	32 to 51	24 hrs.–5 days	Injection—Heat	—	—	10
Chronic Bursitis	5	M—4 F—1	27 to 43	1 yr.–8 yrs.	Various—X-Ray—Needling	2	3	—
Myofibrositis	20	M—11 F—9	31 to 47	2 wks.–1 yr.	Multiple	5	10	5
Low Back Distress—Functional	22	M—14 F—8	28 to 53	3 hrs.–1 wk.	Indefinite	4	3	15
Neuralgias—Neuritis, Herpes Zoster	5	M—2 F—3	32 to 55	5 days—3 yrs.	Indefinite	5	—	—
Multiple Sclerosis	2	M—1	32 to 65	2–7 yrs.	Usual Routine	2	—	—

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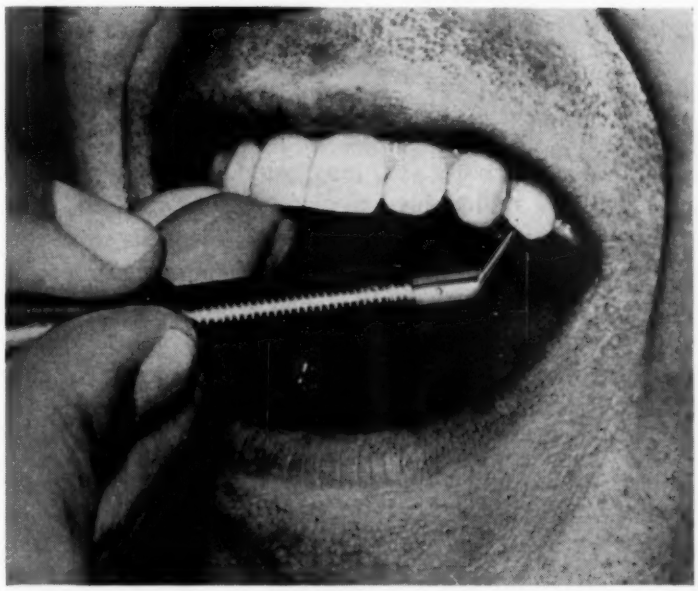

FIG. 4. Illustrating Cavitron ultrasonic dental handpiece.
(Courtesy, Oman, C. B. and Wolff & Associates.)

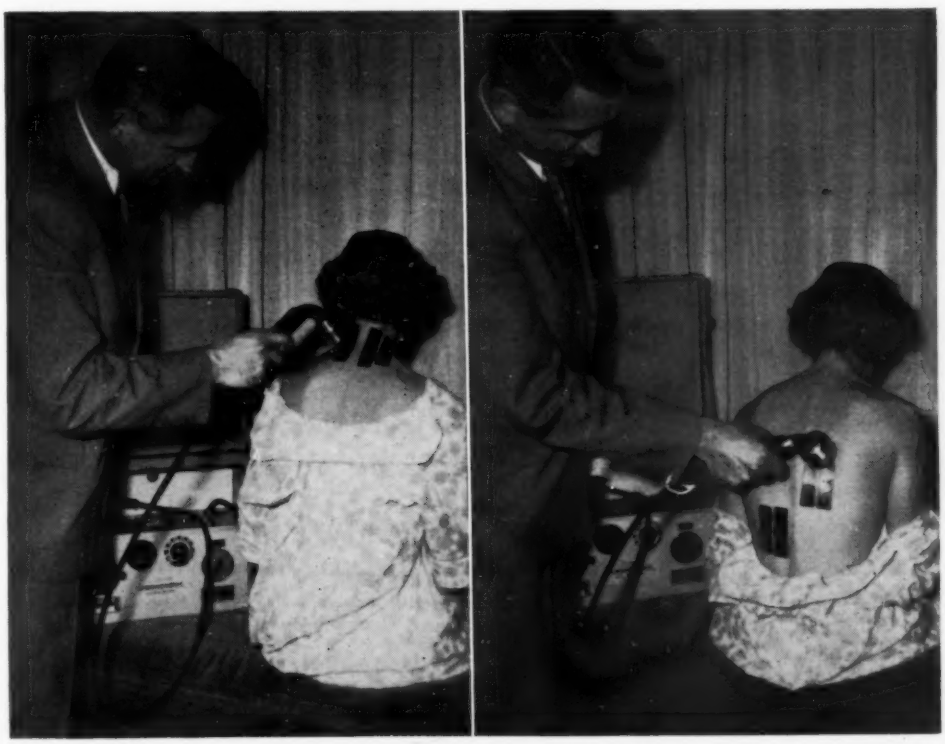

FIG. 5. Illustrating position of soundhead during treatment, and area strips for guidance of operator. (Courtesy, R. J. Lindquist Co.)

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which enables tooth structure to be cut rapidly without pain, heat, noise or vibration.

SAFETY

Questions arise as to the extent of the use of ultrasonic therapy and its safety. The following analysis by Bauer (18) may provide adequate answers. In 1953 a survey by questionnaire, under the direction of Stuhlfauth and Woeber, brought replies from 285 medical practitioners and 27 hospitals and clinics, covering 101,629 case reports. An Austrian clinic reported some reaction two or three days after treatment. About 10 replies mentioned restlessness, giddiness or nausea, and lowering of blood pressure in patients with a labile autonomic nervous system. As the balance of the replies contained no reference to side-actions, the inference is that ultrasonic applications, properly used, are free from danger.

Some areas are best avoided—the eye, the pregnant uterus, and the growing centers of young bones. Some clinicians are fearful of applying ultrasound waves to the stellate ganglion, but others are treating this area with no adverse reactions.

A thorough comprehension of the physiology and dosage involved is the guideline to safety. Dosage includes not only watts and the time of exposure, but also the technic of application (Fig. 5). A recent report (29) devoted to the latter phase should be studied carefully.

SUMMARY AND COMMENT

Ultrasound energy is now established as a safe and valuable agent in therapeutics. Possibilities for its use in diagnosis continue to unfold. This energy can be beamed. It penetrates deeply, but it is not radiation in the sense of x-rays which strike at the nuclei of cellular structures. It is neither electrical nor chemical, although it is believed to act as a catalyst to chemical reactions.

The engineering construction of the unit is important, as it lends itself in a vital way to the problems of dosage and technical application. Although there is a thermal component to the biologic action of ultrasound waves, a nonthermal component also exists, probably related to intracellular and neural metabolism.

The established clinical indications have been outlined. Possible contraindications are few in number. Like other physical energies, ultrasound waves carry potential power and must be kept within established therapeutic bounds. The possibilities of this agent in geriatrics, particularly as applied to dentistry, have been presented.

Acknowledgment

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ATHEROMATOUS AND ESSENTIAL BENIGN HYPERTENSION—TWO CLINICAL ENTITIES: DIFFERENTIAL DIAGNOSIS AND TREATMENT*

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It is well known that hypertension manifests itself in many pathologic conditions and deranged physiologic states.

From our studies it appears that there is a distinct difference between "essential benign hypertension" and hypertension seen as a sequela of atheromatous cardiovascular disease. The latter form should be designated as "atheromatous hypertension." In some instances these two types may co-exist. The reason for differentiating the two forms of hypertension will become clearer as we proceed with this presentation.

Although the height of the blood pressure in essential hypertension is an important index of the severity of the disease, this is only relatively true when the blood pressure is found to be elevated in atheromatous individuals. The use of hypotensor drugs for reduction of blood pressure levels in essential hypertension, which we would prefer to designate as arteriolar hypertension, offers symptomatic relief and prolongs life. However, their employment as therapeutic agents in atheromatous hypertension, from our observation, is highly questionable.

Atherosclerosis per se is neither a cause nor a direct result of hypertension. This is borne out by the fact that many patients who have advanced atherosclerosis, proven clinically and at necropsy, have at no time shown elevation of blood pressure. It appears, therefore, that hypertension may be a complication only in some atherosclerotic individuals. The abdominal aorta is usually the site of predilection in atherosclerosis, which is becoming recognized as a systemic disease (1). It makes its first appearance above the bifurcation of the abdominal aorta and at times extends beyond the renal arteries. This is a consistent finding. If atherosclerotic changes are observed in arteries such as the coronary, cerebral or peripheral blood vessels, without involvement of the abdominal aorta, they may be due only to local tissue irritation secondary to infection, chemical injury, trauma, or other vascular pathologic conditions in which the continuous process of repair is disturbed. Thus, an artery may become predisposed to lipid deposits in the absence of systemic manifestations of atherosis, in the presence of normal blood cholesterol levels, normal lipoprotein patterns and a negative family history.

In many individuals in whom the abdominal aorta shows necrotic and atheromatous patches, the kidneys often are found to be covered with scars and de-

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pressions. The extent of the renal involvement does not always parallel the degree of atherosclerotic involvement of the abdominal aorta. The renal capsule in these cases is adherent to the ischemic infarcted areas. Allbutt (2) described the condition of the arteries in such a kidney as the "decrescent type of arteriosclerosis." The kidney is smaller and softer to touch than that in essential hypertension. The renal artery is atheromatous. We believe these ischemic areas to be the cause of bouts of hypertension in the atheromatous subject, if the infarct is sufficiently large. This concept of atheromatous hypertension would tie in with observations by Janeway (3) and Goldblatt *et al.* (4). They showed that hypertension may be produced by clamping of the renal artery. This phenomenon has been attributed by them to a vasopressor substance excreted by ischemic renal tissue. The acute phase of atherosclerotic thrombosis of the renal artery has been described by us as a clinical entity (5, 6).

In essential hypertension, on the other hand, the renal picture is strikingly different (7). Although the small arteries of the brain, retina, spleen and even

TABLE 1

Differential Diagnosis

Atheromatous Hypertension	*Essential Benign Hypertension*
Retinal vessels somewhat tortuous; no papilledema observed.	Retinal vessels show disproportion of the caliber of arteries to veins. Papilledema in severe cases.
Pulsations of dorsalis pedis and posterior tibial arteries often impaired.	Pulsations in lower extremities, usually of excellent quality.
Supracardiac area of dullness increased.	Supracardiac area of dullness within normal limits.
Left ventricular hypertrophy, left axis deviation and left ventricular strain not marked; occur rarely and then only in the advanced stage.	Occur frequently and comparatively early.
Roentgenogram of abdominal aorta reveals atherosclerotic changes in most cases.	Atherosclerotic changes visualized only when atherosclerosis and e. b. hypertension co-exist. If present, they are of a negligible degree.
Coronary insufficiency and cerebral vascular involvement appear late.	Seen comparatively early.
Sequelae of obliterative peripheral vascular disease frequently encountered.	Extremely rare.
Xanthomata, particularly xanthoma palpebrarum, frequently seen.	Very rare.
Usually normotensive, even hypotensive. May experience sudden bouts of hypertension after years of "low blood pressure." Self-regulative, after interval.	Blood pressure fluctuations are common. History shows consistent trend to high blood pressure.
On pathologic examination, kidneys small and soft and covered with scars and depressions. Renal artery is atheromatous. Scarring is attributable to infarction resulting from focal atherosclerosis obliterans.	Renal picture due to arteriolar involvement. Effect on kidney depends entirely on extent and intensity of vascular lesions.

skeletal muscle (8) often are involved, renal damage occurs without exception (9).

When the capsule is stripped, the entire kidney appears to be truly granular. Upon histologic examination the arterioles are found to be hyperplastic—hence the term "hyperplastic arteriopathy" (10). There is a uniform hyaline thickening of the subendothelial layers of the intima in the arterioles.

Although it takes an exceptionally well trained pathologist with particular interest in vascular diseases to differentiate between renal damage in essential hypertension and in atheromatous hypertension, differentiation of these two types is less of a problem for the clinician.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis between atheromatous and essential benign hypertension is not too difficult (Table 1).

Although the retinal vessels are somewhat tortuous in the atheromatous subject, in the patient with essential benign hypertension there is a disproportion of the caliber of arteries to veins. When the hypertension is severe, nicking at the arteriovenous crossings is a common finding. Papilledema, seen in severe hypertension, has not been observed by us in atherosclerotic subjects.

Pulsations of the dorsalis pedis and posterior tibial arteries often are impaired in the atheromatous group but are of excellent quality in the essential group.

FIG. 1. Appearance of supracardiac shadow in atheromatous hypertension

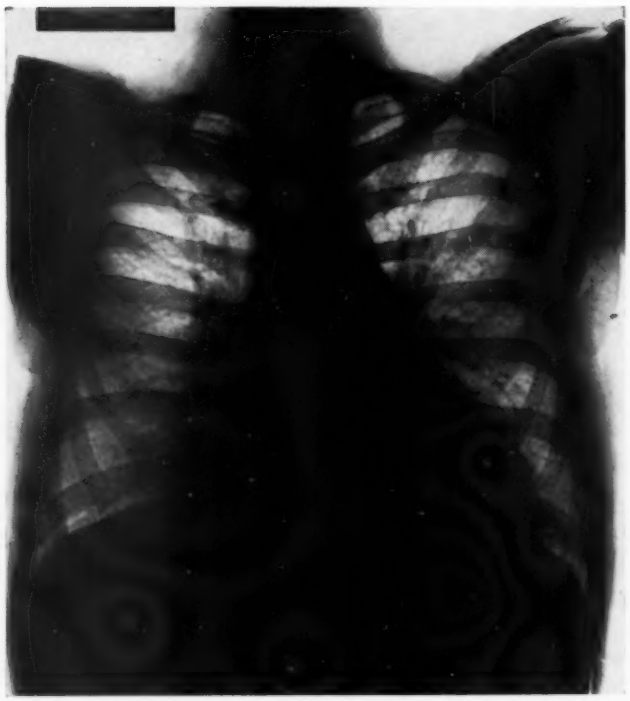

FIG. 2. Appearance of supracardiac shadow in essential hypertension

FIG. 3. Atherosclerotic changes of the abdominal aorta (lateral Bucky roentgenogram).

FIG. 4. Lateral roentgenogram of the abdominal aorta in essential hypertension.

The supracardiac area of dullness often is increased in the atheromatous subject due to uncoiling of the aorta (Fig. 1) but is usually within normal limits in essential hypertension (Fig. 2). Left ventricular hypertrophy, left axis deviation and left ventricular strain are more marked in the essential hypertensive group. Should these occur in the atheromatous group, they make their appearance at a more advanced age level—usually in the sixth decade.

Atherosclerotic changes in the abdominal aorta visualized by a lateral roentgenogram (Fig. 3) are present in the majority of atheromatous subjects. Such changes are infrequently seen in the essential hypertensive group (Fig. 4). If the two conditions co-exist, atheromatous changes of the abdominal aorta may be present in the essential group but only to a negligible degree. Coronary insufficiency and cerebral vascular involvement are seen comparatively early in the essential group, whereas they make their appearance much later in the atheromatous group. Manifestations resulting from obliterative peripheral vascular disease are encountered frequently in the atherosclerotic subject but are extremely rare in the patient with essential hypertension. Xanthomata, particularly xanthoma palpebrarum, are a frequent occurrence in atheromatosis and much rarer in essential hypertension.

Usually the atheromatous subject is normotensive or even hypotensive, but may experience a sudden bout of hypertension lasting from several months to several years, after which time he may again become normotensive. Such an individual may register surprise when hypertension is discovered and state that for years he had been "treated for low blood pressure." The history is entirely

different in the essential group. Although fluctuations in the degree of blood pressure elevation are common, the patient is aware of a tendency toward elevated blood pressure, because of the findings on previous examinations.

In a series of 1,000 consecutives cases of clinically proven atherosclerotic subjects at the Valley Forge Heart Institute and the Wolffe Clinic, 27 per cent had an elevated blood pressure at the time of our examination, as judged by Master's standards (11).

THERAPY

Fifty of our atherosclerotic patients in this series received sympathicolytic drugs such as hexamethonium, 1-hydrazinophthalazine hydrochloride (Apresoline), *Rauwolfia serpentina*, or *Veratrum viride*. In 8 of this small series thrombotic phenomena developed when blood pressure levels were effectively lowered. A distinct relationship appeared to exist between the lowering of blood pressure levels and cerebral vascular thrombosis in 6 cases, coronary thrombosis in 1 case, and popliteal artery thrombosis in 1 case.

It stands to reason that increased pressure encourages blood flow in an atheromatous artery. If the pressure is lowered to unaccustomed levels, the blood flow may become inadequate and may hasten the occlusive phase of atherosclerosis. We were sufficiently impressed by these untoward effects to have a standing rule not to administer hypotensor drugs to atherosclerotic patients of the older age group—except for nitroglycerine or amylnitrite, the effects of which are of very short duration.

In atheromatous hypertension the aim is to treat what we believe to be the underlying cause—a disturbance of lipoid metabolism. Low-cholesterol diets, with adjustment of caloric intake according to the patient's need, are recommended. Physical activity within the limits of each individual's capacity is *encouraged*. The use of pancreatic extracts is beneficial. Intravenous administration of alcohol-ether with coenzymes in atherosclerosis obliterans has proved to be a valuable adjunct in the treatment of some of these patients (12).

As previously noted, the use of hypotensor drugs in atheromatous hypertension in the elderly patient may do more harm than good. It may predispose to obliterative vascular complications. In the treatment of essential hypertension, on the other hand, great progress has been made since the advent of sympathicolytic drugs. A polypharmaceutical approach yields the best results (13). The combination of hexamethonium compounds with *Rauwolfia serpentina*, 1-hydrazinophthalazine hydrochloride, and sedatives, adjusted gradually to each patient's need, is very beneficial. Unfortunately, careful dosage adjustment is often made impossible by the present-day method of drug marketing. Medication is supplied in tablets of a predetermined dosage rather than in bulk. The American Therapeutic Society should adopt as one of its projects a drive to persuade drug firms to supply medication in bulk so that we in turn may be able to write prescriptions suitable for each individual, as practiced by our fathers.

SUMMARY

The differential diagnosis of atheromatous hypertension (post-thrombotic renal-artery hypertension) and essential hypertension (arteriolar hypertension) is discussed. Differences in management of these two hypertensive states are enumerated and possible contraindication to the use of hypotensor drugs in atheromatous hypertension is stressed.

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A FIVE-YEAR STUDY OF ADRENAL STEROID COMPOUNDS*

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My subject concerns one of the most fascinating chapters in the history of medicine. It was my pleasure to hear Dr. Hench's original presentation of the use of cortisone before the International Congress of Rheumatic Diseases in New York in 1949 and also Reichstein's original presentation on electrocortone at the International Congress of Rheumatic Diseases in Geneva in 1952. The original dose of cortisone was 200 mg. the first day, 200 mg. the second, and 100 mg. daily thereafter, according to the amount necessary for control of the disease. In our initial work, we followed this dosage schedule but soon found it unsatisfactory. In October 1950 (1) we pointed out the dangers of this method and suggested that therapy should be started with a small dose until the individual's tolerance could be appraised and his optimum dose determined. Except in rare instances, or when it is necessary to control a disease rapidly (as in rheumatic fever) this routine should be followed. We seldom give more than 50 to 75 mg. as a maintenance dose and most often it ranges from 37½ to 62½ mg. of cortisone, and from 30 to 50 mg. of hydrocortisone. In patients with arthritis, we do not give enough to keep them symptom-free but only enough to enable them to be comfortable and continue their occupations. In rheumatic fever, however, one should endeavor to suppress the disease as rapidly as possible and maintain absolute control until the attack is aborted; the duration may vary with each patient. In this instance, the eosinophil count is a valuable criterion and should be maintained below 5 if possible, and certainly below 10.

CORTISONE—SIDE EFFECTS AND GENERAL CONSIDERATIONS

I. *Sodium retention*

A sodium-free diet is not necessary in most instances, but sodium restriction is advisable and it is important to warn patients about taking alkalies containing sodium. There is very little difficulty with sodium retention under a small maintenance dose.

II. *The effect upon glucose metabolism*

We have not encountered a true case of diabetes that could be attributed to cortisone, but this may be due to the small dose used. We have had patients in whom the blood sugar level gradually rose from 110 to 140 mg. per 100 ml., but returned to normal as soon as cortisone was omitted. In 2 instances, the

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blood sugar level was markedly elevated and there was sugar in the urine. It took several days after omitting cortisone before the blood sugar concentration returned to normal. No hyperglycemia persisted beyond four weeks, however.

III. *Hirsutism*

This is occasionally a troublesome symptom but fortunately does not occur often. In some women it will occur during administration of only 37½ to 50 mg. daily. Cortisone should be omitted in these instances.

IV. *Moon-face or Cushing's syndrome*

When this occurs the cortisone should be reduced or omitted. After a period without medication, the moon-face may be considerably lessened and cortisone may be resumed.

V. *Gastro-intestinal irritation*

There may be distention and flatulence, reactivation of ulcers, and hemorrhages. Patients with a history of ulcer or healed ulcer should not be given cortisone if it can be avoided.

VI. *Psychiatric and neurologic manifestations*

There were no severe mental or neurologic symptoms in our series. Some patients complained of insomnia, tremor of the hands, inability to concentrate, and being jittery, but this occurred mostly in those receiving 75 mg. or more daily. Persons with a psychiatric history should not be given cortisone. In patients who are emotionally unstable, it should be given in small doses until the reaction can be determined. If psychiatric symptoms develop, it should be omitted immediately. If euphoria develops, the dose should be reduced and the patient watched carefully. Those who are inclined to be depressed, particularly women during the menopause, should be given small doses. If these rules are followed, nervous or mental complications will be insignificant.

VII. *Cardiovascular symptoms*

The importance of cardiovascular symptoms in cortisone-treated patients was pointed out five years ago (1), and again I wish to emphasize their importance. Cortisone in the younger age group is seldom dangerous, but in the older age group, particularly in persons with mild to moderate hypertension, severe complications may arise. In our series, a rise in blood pressure occurred in many in the older age group; some patients had an initial rise of 20 to 40 points but the pressure returned to normal even though cortisone was continued. In others the blood pressure became stabilized at this level, but in a few continued to rise and increased as much as 100 points. Small doses of a sedative given three or four times daily helps to prevent some of the increases in blood pressure. Recently one of the Rauwolfia preparations has been used in this group and blood pressures have returned to normal in several instances.

VIII. *Thromboembolic phenomena*

The thromboembolic phenomena are more serious than the increased blood pressure. Some patients have had cerebral thrombosis, coronary occlusion, mesenteric thrombosis, thrombosis of the popliteal artery and thrombophletitis, apparently precipitated by cortisone therapy.

SIMULTANEOUS ADMINISTRATION OF CORTISONE AND ANTICOAGULANTS

Cosgriff (2) in 1950 reported that in a large proportion of patients receiving the steroid compounds, there was a definite reduction in the venous and heparin-retarded clotting times. We confirmed this observation, and decided that if we were not to submit these patients to added risk, we must find some way to prevent the increased thromboembolic phenomena. This suggested the use of anticoagulants simultaneously with the cortisone. Dicumarol, perhaps the most widely used anticoagulant at that time, did not appear to be suitable for our purposes, as it required almost daily checking because of the wide fluctuation in prothrombin times that occurred with its use. However, the reports of Jaques *et al.* (3), Blaustein *et al.* (4) and others suggested the possibility that the phenylindanedione group might be suitable.

The preparation used was phenindione.[1] Therapeutic effects may be obtained with phenindione within eighteen to twenty-four hours and the prothrombin time returns to normal within thirty-six to seventy-two hours after omitting the medication. In ambulatory office or clinic patients, the initial dosage is 20 mg. of phenindione and 20 mg. of hydrocortisone[2] twice daily. The patient returns in a week for determination of the prothrombin time. The administration is then regulated according to the needs of each patient, and the material should be given in two or three doses daily. There have been no undesirable effects from a dosage of 20 mg. twice a day. We have been impressed with the constancy of the prothrombin time once the maintenance dose has been established for each individual, and believe that the phenindione can be given to ambulatory patients without much danger. However, there is a wide variation in the maintenance dose in different individuals. In some patients the prothrombin time remains normal, even though the dose is as large as 100 mg. of phenindione daily. In other patients, 40 to 60 mg. daily will increase the prothrombin time to twice normal (Tables 1 to 5). One technician was responsible for most of the prothrombin time determinations, and the results were double checked in most instances. Simplastin and Diagnostic Plasma were used for these determinations.[3]

In over two years' study of 200 patients receiving phenindione and 70 patients receiving phenindione and cortisone combined, we have observed only 1

[1] This study was supported by a grant-in-aid by Walker Laboratories. This firm also contributed the phenindione (Hedulin).

[2] The hydrocortisone used in this study was contributed by Merck & Co.

[3] The Simplastin and Diagnostic Plasma were contributed by Warner- Chilcott.

TABLE 1

Patient: BL

Date	Prothrombin Time (secs.)		Dosage of Phenindione (mg.)
	Control	Patient	
October 13	12.5	15	200 daily
October 14	15	26	100 daily
October 15	15	24	100 daily
October 16	15	30.5	75 daily
October 17	15	28	100 daily
October 19	15	25	100 daily
October 20	15	24.5	100 daily
October 21	12	21.5	100 daily
October 22	14	23.5	100 daily
October 24	12.5	23	100 daily
October 26	12	23	100 daily
October 28	13	24	100 daily
October 29	12	24	100 daily

TABLE 2

Patient: Mr. H.

Date	Prothrombin Time (secs.)		Dosage of Phenindione (mg.)
	Control	Patient	
Jan. 21	12	13	20 t.i.d.
26	15	21	20 t.i.d.
Feb. 9	13.5	20.5	20 t.i.d.
16	12	21.5	20 t.i.d.
23	13.5	19.	20 t.i.d.
Mar. 2	13.5	19.	20 t.i.d.
9	14	19.5	20 t.i.d.
23	12.5	19.	20 t.i.d.

TABLE 3

Patient: MD (age 59)

Date	Prothrombin Time (secs.)		Dosage (mg.)	
	Control	Patient	Ph enindione	Hydrocortisone
Jan. 4	13.2	13.5	25 t.i.d.	62.5 daily
15	12.8	20.2	25 t.i.d.	62.5 daily
22	12.8	24.0	25 t.i.d.	62.5 daily
29	13.3	21.3	25 t.i.d.	62.5 daily
Feb. 5	12.7	20.8	25 t.i.d.	62.5 daily
11	13.2	20.6	25 t.i.d.	62.5 daily
18	12.2	16.7	25 t.i.d.	62.5 daily
Mar. 5	13.8	17.7	25 t.i.d.	62.5 daily
12	13.5	19.1	25 t.i.d.	62.5 daily
19	12.5	19.	25 t.i.d.	62.5 daily

TABLE 4
Patient: FS (age 84)

Date	Prothrombin Time (secs.)		Dosage (mg.)	
	Control	Patient	Phenindione	Hydrocortisone
Apr. 4	11.9	12.2	40 daily	
13	13.5	17.5	40 daily	
27	12	22	100 daily	75 daily
May 18	13	19.5	60 daily	
June 8	12.5	19.5	60 daily	75 daily
July 6	14.5	19	60 daily	75 daily
27	15	15.5	80 daily	75 daily
Sept. 7	14	16.5	80 daily	75 daily
28	15	17	80 daily	60 daily
Nov. 23	13.5	20	—	60 daily

incident of significant bleeding. This was renal bleeding which occurred when, due to a misunderstanding, the dose of phenindione was increased from 80 to 200 mg. daily. The patient was given vitamin K (70 mg. intramuscularly twice in the first twenty-four hours) and the prothrombin time dropped from 42 to 32 seconds within twelve hours. Within thirty-six hours, the prothrombin time was 18, the control 14 seconds, and the bleeding had decreased by 50 per cent. The patient was given 70 mg. of vitamin K during the second twenty-four hours. All major bleeding had ceased forty-eight hours after omitting the phenindione and the prothrombin time was normal. Sixty hours after the phenindione was omitted, all bleeding had stopped. The blood count remained within normal limits. Two patients had mild bleeding from hemorrhoids. Although there was a history of previous bleeding, phenindione apparently precipitated the episode

TABLE 5
Patient: SO

Date	Prothrombin Time (secs.)		Dosage of Phenindione (mg.)
	Normal	Patient	
Mar. 5	14	15.5	300 daily
16	12	19	100 daily
18	14.5	26	175 daily
20	15	31	150 daily
22	14	28	150 daily
25	13.5	29	150 daily
29	14.5	35.5	150 daily
Apr. 1	14	32.5	150 daily
8	13.5	36.5	125 daily
13	13.5	28	125 daily
22	14.5	32	125 daily
May 3	13	35	125 daily
10	15	33.5	125 daily

and perhaps should not have been given. It should not be given when there is a history of ulcer of the stomach, ulcerative colitis, or even a severe colitis. Each patient should receive a card outlining his anticoagulant therapy, and warning that an immediate check should be made in case of trauma or emergency surgery.

In 5 patients receiving cortisone, thrombophlebitis of the lower extremities developed. One was a man, aged 63, with severe rheumatoid arthritis. He had four attacks of acute thrombophlebitis involving the left saphenous vein, and was hospitalized on two occasions. The fourth time he had not improved and the condition had persisted for several weeks. He was unable to carry on without cortisone and he was given phenindione simultaneously. The arthritis remained under control and there was gradual improvement of the thrombophlebitis. Within three weeks, almost all the symptoms had subsided. He has not had another attack of thrombophlebitis to date, although the cortisone has been continued for eighteen months. A women aged 24 years had arthritis since the age of 18. After receiving cortisone for three years, thrombophlebitis developed in the right saphenous vein. The cortisone was continued but phenindione was added. The thrombophlebitis gradually improved and in four weeks she was entirely symptom-free. Phenindione was continued for three months. In fifteen months there has been no return of the thrombophlebitis, although she has continued the cortisone. We do not advocate administration of anticoagulants in every patient receiving cortisone, but only in those who have or have had evidence of thromboembolic phenomena and in those with hypertension and/or arteriosclerosis. Elderly patients are more susceptible to thromboembolic disturbances when receiving cortisone, particularly when it is continued for a long period of time. Anticoagulants will not prevent all thromboembolic phenomena but will decrease the incidence. Apparently it is not necessary to maintain the prothrombin time at 2 to 2½ times normal for this purpose; a 50 to 70 per cent increase is sufficient. In 70 patients all over 55 years of age, treated with cortisone and phenindione for a period of time ranging from three to eighteen months, there has not been 1 instance of thromboembolic phenomena.

THE ADRENAL GLAND DURING STEROID THERAPY: THE EFFECT OF ACTH

As our experience with cortisone increased, it became evident that a chemically induced adrenal atrophy and insufficiency occurred, and this raised many important clinical problems. It seemed important, therefore, to determine experimentally 1) whether or not it was possible to induce adrenal regeneration, once atrophy had occurred, even though cortisone was continued, and 2) more important still, whether the simultaneous administration of ACTH and cortisone would prevent adrenal atrophy.[4] Because of the clinical interest in com-

[4] A full report appeared in an article by Rawls *et al.*: *J. Lab. & Clin. Med.* **44:** 506, 1954; any part thereof repeated here is by the courtesy of that journal.

pound F (hydrocortisone) and compound B (corticosterone) at the time this work was in progress, the experiment was expanded to include these materials.

In the rat, each of the three steroids caused a loss of approximately 20 per cent of the total body weight in fifteen days, whereas with ACTH the loss was only 4 per cent. However, when ACTH and a steroid were given conjointly, the weight loss did not exceed that caused by the administration of steroid alone, although these animals appeared to be in far worse physical condition.

Prolonged cortisone treatment did not further reduce the weight of the atrophic post-hypophysectomy adrenal and there was no alteration of the cholesterol concentration as a result of such treatment. The other adrenal steroids tested by us likewise failed to influence adrenal weight in hypophysectomized animals. One compound (corticosterone) did affect the cholesterol concentration.

Lewis *et al.* (5) in 1950 found that cortisone did not cause alteration in adrenal weight or adrenal cholesterol concentration in rats maintained continuously with ACTH after hypophysectomy. This is strong evidence in favor of the clinical advantages of simultaneous administration of ACTH and compounds of the cortisone group. From our point of view, however, it was important to discover whether adrenal regeneration could be brought about during cortisone therapy, and for this reason our experiments differed from those of Lewis *et al.* in the sense that adrenal atrophy was allowed to develop before treatment was instituted. The data obtained indicated clearly that adrenal regeneration induced by ACTH is unaffected by the concomitant administration of an adrenal steroid. Furthermore, it was demonstrated that the atrophied adrenal gland could be returned to approximately its normal weight, even though cortisone was continued. The occurrence of adrenal atrophy following prolonged cortisone therapy suggested to us that if this medication was omitted during a period of stress and strain, the patient would be subjected to the added danger of shock, or even irreversible shock. Therefore, in October 1952, it was suggested that cortisone be continued during stress periods. It was further suggested that each patient receiving prolonged treatment with cortisone should carry a card stating the amount taken and warning against discontinuing it in times of stress (6). Since that time, other workers in the field have adopted this routine (7). We have shown that ACTH will restore the adrenal gland to almost normal weight, even though cortisone is continued. However, the problem is in what dosage, and how often must ACTH be given in order to prevent adrenal atrophy. We are now studying the urinary 17-ketosteroids in 50 of these patients. We do not have determinations on all patients prior to cortisone therapy, as some were receiving cortisone before this study was begun. However, there were definite changes in some patients. For example, before cortisone therapy, the urinary 17-ketosteroids were 9.3, 10.9 and 7 mg. per twenty-four hours respectively in 3 male patients (by our method, the normal for males is 7 mg. or over); after cortisone therapy (60 mg. per day for three months) the ketosteroids were 3.7, 2.1 and 3.6 mg. per twenty-four hours respectively. This was definitely below normal and perhaps indicates adrenal atrophy. In 3 other

male patients the 17-ketosteroids were 2.4, 3.2 and 4.8 mg. after cortisone therapy, and these values were increased to 6.9, 5.5 and 6.38 mg. after 40 units of ACTH Gel daily for one week, even though cortisone was discontinued during this period. Although 17-ketosteroid determination may not be considered an absolute test of adrenal function, it is safe to conclude that the increased 17-ketosteroid excretion observed indicates an increase in adrenal function. This would correspond with our observations that the weight of the atrophied adrenal glands in rats may be increased, even though cortisone is continued. We do not know the correct dosage for counterbalancing the effect of the cortisone upon the adrenal gland, but this work is continuing and we hope to obtain more definite information.

THE RETICULO-ENDOTHELIAL SYSTEM DURING CORTISONE THERAPY

The question of resistance in cortisone-treated patients has evoked much discussion and many opinions, but it seems to be fairly well agreed that cortisone does lower the resistance to tuberculosis. In 1951 Lurie and co-workers (8) reported an interesting phenomena. Using a quantitative technique (the weight of India-ink particles retained by the liver and spleen three hours after intravenous injection), they observed that in the rabbits treated with cortisone (1 mg./Kg./day) phagocytosis was decidedly greater than in the controls. More revealing still were observations following the administration, by inhalation, of human-strain tubercle bacilli. It was found that, although phagocytosis of the tubercle bacilli was greater in the treated rabbits, pharmacologic doses of cortisone interfered appreciably with the capacity of the macrophages to digest the trapped bacilli.

In conjunction with other studies on the mechanism and possible prevention of the deleterious effects which sometimes accompany the therapeutic use of massive doses of adrenal steroids, we studied the India-ink uptake of the reticulo-endothelial system with qualitative and quantitative techniques[4].

Our observations that large doses of various steroids did not depress the India-ink uptake below that of the intact animal, and those of Lurie *et al.* that after treatment with cortisone there was a decidedly greater phagocytosis for India ink and tubercle bacilli than in the normal animal, furnished suggestive evidence that cortisone and similar compounds do not depress the phagocytic ability of the macrophages. The reticulo-endothelial system is known to behave differently with different substances and our results with India ink do not necessarily agree with those obtained by using Thorotrast or other materials. Moreover, no one substance can or should be interpreted as capable of demonstrating the totality of reticulo-endothelial phagocytosis as it occurs *in vivo*.

If cortisone does not reduce the phagocytic ability of the macrophages, then there must be another reason for its effect in lowering resistance to certain infections. Perhaps this reason may be found in the observation of Lurie *et al.* that following the inhalation of human tubercle bacilli, the phagocytosis of the bacilli was increased, but the ability of the macrophage to digest the bacilli was appreciably diminished in the cortisone-treated animal. These phenomena may

more truly represent the physiologic pattern. On this basis, it appears that the resistance mechanism does not depend on phagocytosis alone and that the phagocytic activity of the macrophage may be as great in the cortisone-treated animal as in the intact animal, or even greater. Therefore, the fact that the India-ink uptake is approximately the same in hypophysectomized animals receiving large doses of ACTH or steroids, alone or simultaneously, does not necessarily mean that the resistance of the three groups is the same. Since during the administration of ACTH to the hypophysectomized animal the adrenal weight returns to an approximately normal level, the question arises as to whether ACTH administered simultaneously with the steroids will maintain the ability of the macrophage to digest the invading organism to the same extent as in the intact animal. If so, it is possible that the simultaneous administration of ACTH with the adrenal steroids may maintain a normal degree of resistance during prolonged treatment with cortisone.

These are only a few of the problems involved in cortisone therapy. There is a great deal to be learned and much work to be done.

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Obituaries

WILLARD OWEN THOMPSON

Doctor Thompson, better known all over the country as "Willard," died March 23, 1954 at Henrotin Hospital in Chicago. Death came as the result of cerebellar hemorrhage and brought to an end a most colorful and brilliant medical career. He always had time for one more task and he always did it well, even though his work day already extended long hours.

The American Therapeutic Society was served by him as a council member and a former vice-president. He gave several papers on endocrinology before the society. His stories and his flair for entertaining most royally will long be remembered by its members.

His curriculum vitae as it appeared in the Journal of the A.M.A. follows:

Doctor Thompson was born in Fredericton, New Brunswick, Canada, February 17, 1899, and came to the United States in 1920. After graduation from Harvard Medical School, Boston, in 1923, he served an internship at the Boston City Hospital from 1923 to 1925. From 1926 to 1928 he was a fellow of the National Research Council. He was research fellow in medicine at his alma mater from 1925 to 1928, Henry P. Walcott fellow, 1928–1929, and in 1927 assistant in Chemistry. In 1925 he was graduate assistant in medicine at the Massachusetts General Hospital in Boston, where from 1926 to 1929 he was research fellow in medicine and also in charge of the metabolism laboratory. Doctor Thompson came to Chicago in 1929 and joined the faculty of Rush Medical College as assistant clinical professor, serving in that capacity until 1935, when he became associate clinical professor. At the time of his death he was clinical professor of medicine at the University of Illinois College of Medicine, where he was associate professor of medicine from 1941 to 1943 and professor of medicine from 1943 to 1945. Doctor Thompson was a specialist certified by the American Board of Internal Medicine and by the National Board of Medical Examiners. He was the current president of the American Geriatrics Society, and held presidential and various other offices in the Chicago Medical Society, the American Goiter Association and the Mississippi Valley Medical Society. In 1944–1945 he was vice-chairman of the Section of Medicine of the American Medical Association. In 1952 he earned the distinguished service award of the Mississippi Valley Medical Society for rendering unusual and distinguished service to the medical profession. He was a member and had held offices in the Endocrine Society, was a Fellow of the American College of Physicians, and a member of the American Society for Clinical Investigation, Association of American Physicians, Society for Experimental Biology and Medicine, American Diabetes Association, Central Society for Clinical Research, American Heart Association, American Association for the Advancement of Science, World Medical Association, Gerontological Society, Society for Research in Child Development, American Association of the History of Medicine, American Society for Study of Sterility, American Psychomatic Society, Association of American Medical Colleges, American Medical Writers' Association, Illinois State Academy of Science, Institute of Medicine of Chicago, Sigma Xi, Pi Kappa Epsilon, Chicago Society of Internal Medicine, Society of Medical History of Chicago, and the Chicago Association of Commerce and Industry. The Commanding General of the Sixth Service Command awarded him a certificate of distinguished service in 1945 for his untiring efforts and devotion as chairman of the regional Committee for Wartime Graduate Medical Meetings. From 1934 to 1940 he was research associate in pathology at Cook County Hospital, and was associate attending

physician at Presbyterian Hospital until 1946. Since 1947 he had been attending physician at Grant Hospital and Henrotin Hospital, and since 1945 he had been attending physician at the University of Illinois Research Hospitals. Doctor Thompson was editor of "American Lectures in Endocrinology," the Journal of the American Geriatrics Society, formerly editor of the "Year Book of Endocrinology," and since 1946 managing editor of the Journal of Clinical Endocrinology and Metabolism. He was on the editorial board of the Mississippi Valley Medical Journal, American Practitioner, and GP and contributed numerous scientific articles to medical publications and textbooks.

THOMAS COOGAN, M.D.
Chicago, Illinois

ROBERT JOHNSON WILKINSON

Robert Johnson Wilkinson was born in Campbell County, Virginia, July 12, 1888, the son of Beverly Jasper and Sarah Jane Traylor Wilkinson. His father was an attorney and a Confederate veteran, having served with Mosby's Rangers in the Ohio raid. His preliminary education was in the public schools and at the Mary Agnes Institute, and his professional education at the Medical College of Virginia, where he graduated in 1912. He interned at the Memorial Hospital, Richmond, and then was associated in general surgery with the late Dr. Claude C. Coleman until October, 1915, when he came to Huntington as surgeon-in-charge of the Chesapeake and Ohio Hospital.

Dr. Wilkinson was very active in medical organization work. He was a member of the county, state and national associations, the Southern Medical Association, the World Medical Association, the Association of Surgeons of the Chesapeake and Ohio Railway, the Southeastern Surgical Congress, the American Therapeutic Society, and the Alumni Association of the Medical College of Virginia. He was a fellow of the American College of Surgeons and of the International College of Surgeons, and was a foundation member of the American Board of Surgery. He was the guiding spirit in the formation of the Medical Review Society of Huntington. He served as president of the Cabell County Medical Society, the Association of Surgeons of the Chesapeake and Ohio Railway, the Alumni Association of the Medical College of Virginia, the West Virginia State Medical Association, the Southern Medical Association, and the Southeastern Surgical Congress, and, at the time of his death, was a director of the World Medical Association.

After his location in Huntington, Dr. Wilkinson's whole life was a part of West Virginia medicine. A pioneer surgeon, a careful student, an earnest advocate of better medicine, better surgery and a better profession, he was ever in the vanguard of medical achievement. Reared among the rugged hills of Piedmont Virginia, he was steeped in Jeffersonian philosophy, and was a worthy son of the Old South. Bob, as he was affectionately called by his friends, was throughout the years my friend personally and professionally. He was generous to a fault, a Christian gentleman, a great surgeon, a great human, a great altruist, and truly a great friend of man.

On September 14, 1953 Dr. Wilkinson answered the last roll call, as he had lived, at work. Warm personal friendship and close association with him from boyhood throughout mature life convinces me that we may justly quote the immortal Bard of Avon and say of him:

"His life was gentle, and the elements
So mixed in him, that Nature might stand up
And say to all the world, 'This was a man'."

WALTER E. VEST, M.D.
Huntington, West Va.

JULIAN M. HOWE

Julian M. Howe, Associate Member of the American Therapeutic Society, and general practitioner and surgeon in Washington, D. C. for more than thirty years, died on August 3, 1953, in Miami, Florida, after an illness of several months.

Dr. Howe was born in Worcester, New York, September 17, 1895, the son of John and Jennie Crippen Howe. He came to Washington to study at the Washington Missionary College in Takoma Park, Maryland. Upon graduation from the George Washington University School of Medicine in 1921, he began the practice of medicine in Washington, but later interrupted it to take postgraduate work in surgery abroad at the University of Vienna.

Dr. Howe was an Associate Member of this society since 1934. He was also an Active Member of the Medical Society of the District of Columbia, a member of the American Medical Association, and the Southern Medical Association. He was a veteran of World War I.

Surviving are his wife, Mrs. Rebecca Sevier Howe, of Miami, and two sons, John W. Howe, of Miami, and Carl E. Howe, of Olney, Maryland.

Oscar B. Hunter, Jr., M.D.
Washington, D. C.

REGINALD FITZ

Reginald Fitz was the son of Reginald Heber Fitz, Hersey Professor of the Theory and Practice of Physic at Harvard Medical School and, like his father, was endowed with unusual strength of intellect and personality. He was born in 1885 and at 21 was graduated from Harvard College and at 24 from Harvard Medical School. He served a two-year medical internship at the Massachusetts General Hospital and later became an assistant resident at the newly opened Peter Bent Brigham Hospital, Boston, and at the Rockefeller Hospital in New York City. He was also a volunteer assistant to Dr. William S. Thayer at the Johns Hopkins Hospital in Baltimore. He was a Captain and later a Major in the Harvard Unit in France during the first World War and ultimately served as head of its medical service. In 1918 he married Phoebe Wright, a Canadian physician's daughter, the marriage taking place at Sir William Osler's home in England.

When the war was over Dr. Fitz served on the staff of the Mayo Clinic for two years and at the age of 37 became associate professor of medicine at Harvard Medical School and consulting physician to the Peter Bent Brigham Hospital. He later became Wade Professor of Medicine at Boston University School of Medicine and director of the Evans Memorial and Massachusetts Memorial Hospitals.

His earlier contributions to medicine were concerned chiefly with nephritis and diabetes. Later the profundity and breadth of his intellect were shown by a prolific interest in medical history and medical education. He was assistant dean at Harvard Medical School and marshal at Harvard University. He had an intense interest in the development of the Harvard Medical School Library as well as in the Boston Medical Library and the Army Medical Library at Washington. His medical offices were numerous and included the presidencies of the Massachusetts Medical Society and the American College of Physicians. The breadth of his interest was also shown by his trusteeship of Wellesley College and the Perkins Institute for the Blind and his membership in the American Academy of Arts and Sciences. Devotion to his family, friends and the community in which he lived rounded out a life of singular distinction and value.

SARA M. JORDAN, M.D.
Boston, Mass.

Abstracts of Current Literature

INTERSTITIAL CYSTITIS: A CAUSE OF PERSISTENT BLADDER DISABILITY.

Baker, W. J., and Graf, E. C. *J. Urol.* **72:** 646 (Oct.) 1954.

Debilitating urinary symptoms persisted following prostatic therapy in 7 male patients and were found to be due to interstitial cystitis. The latter was probably present at the original examination but was overlooked when obvious fibrous prostatic sclerosis was found at the bladder neck. Healing of the prostatic fossa following transurethral resection of the prostate gland is accomplished in three months. Symptoms persisting after this time may be due to unrelated pathologic lesions. The bladders in the 7 cases described were irritable. The patients had frequency, nocturia, urgency, and pain. One had acute urinary retention. The diagnosis was established by cystoscopy. Marked improvement followed therapy directed at the relief of the interstitial cystitis.

CALCIFIC AORTIC STENOSIS: STUDY OF SERUM CHOLESTEROL WITH OBSERVATIONS ON CALCIFIC AORTIC STENOSIS IN FAMILIAL XANTHOMATOSIS AND HYPERCHOLESTEREMIA.

Boas, E. P.; Elster, S. K., and Adlersberg, D. *Am. Heart J.* **48:** 485 (Oct.) 1954.

Using Keys' standards, 48.8 per cent of 43 women and 18.6 per cent of 43 men with aortic stenosis had elevated serum cholesterol levels. Among 45 women and 22 men with chronic rheumatic valvular disease, the percentages with hypercholesteremia were 13.3 and 13.6, respectively. By standards derived from a random sample of the population, 53.5 per cent of the women and 27.9 per cent of the men with aortic stenosis were hypercholesteremic. Of those with rheumatic valvular disease 20 per cent of the women and 18.2 per cent of the men were hypercholesteremic. Among the patients with aortic stenosis, 70 per cent appeared to have had previous rheumatic infection. Studies in 3 patients with essential familial xanthomatosis and hypercholesteremia and 1 with familial hypercholesteremia, all of whom also had aortic stenosis, lent support to the view that the elevated serum cholesterol level might be a significant factor in the development of calcific aortic stenosis. All of these findings favor the hypothesis that in individuals with hypercholesteremia aortic stenosis may be caused by atherosclerosis of a normal aortic valve, but that usually it is caused by a secondary atherosclerosis implanted on aortic cusps scarred by ancient rheumatic infection.

CHRONIC BRONCHITIS AND EMPHYSEMA. SIGNIFICANCE OF THE BACTERIAL FLORA IN THE SPUTUM.

Brown, C. C.; Coleman, M. B.; Alley, R. D.; Stranahan, A., and Stuart-Harris, C. H. *Am. J. Med.* **17:** 478 (Oct.) 1954.

1. This study was an effort to obtain data concerning the origin of bacteria in the sputum of patients with chronic bronchitis and emphysema. Of the 16 patients who were bronchoscoped, 8 had similar pathogenic flora in the sputum and bronchial aspirate. The remaining 8 had pathogenic bacteria in the sputum but not in the bronchial aspirate. Possible reasons for this difference are discussed. 2. The data presented do not support the view that organisms in the sputum are derived from the nasopharynx during the process of expectoration. 3. The low incidence of pathogenic bacteria in the sputum of patients with bronchial asthma is important if confirmed in a larger series. (Authors' summary.)

RESPIRATORY ACIDOSIS IN PATIENTS WITH EMPHYSEMA.

Cohn, J. E.; Carroll, D. G., and Riley, R. L. *Am. J. Med.* **17:** 447 (Oct.) 1954.

This report discusses the physiologic mechanisms, clinical appearance, and treatment of respiratory acidosis in 8 emphysematous patients. The disorder should be suspected when bronchopneumonia, severe bronchitis, asthma, or acute heart failure develop in such patients. It may also be indicated by relative immobility of the chest, tachypnea, retraction of the intercostal spaces, marked diminution of breath sounds, inability to raise secretions, and cyanosis. The acid-base patterns in the 8 patients are reported. All suffered from generalized obstructive emphysema. Pulmonary infection and acute heart failure were superimposed in the 5 acute cases and cor pulmonale in the 3 chronic ones. Vigorous treatment with simple and well-recognized measures was successful in the patients with acute respiratory acidosis. It did not, however, reverse the acid-base abnormalities in patients with chronic carbon-dioxide retention. The following elements in the treatment of acute respiratory acidosis are discussed: bronchodilators, antibiotics, oxygen, management of heart failure, mechanical respirators, cortisone and corticotropin, detergents, and helium and oxygen. A combination of factors makes the treatment of chronic respiratory acidosis and the restoration of alveolar ventilation more difficult. Efforts to reduce the work of breathing in these patients should be directed toward increasing the ease with which ventilation can be accomplished. In addition to measures discussed for the treatment of acute respiratory acidosis, pneumoperitoneum, breathing exercises, carbonic-anhydrase inhibitor, and the minimal use of drugs that depress the respiratory centers should be considered in the treatment of chronic respiratory acidosis. Oxygen, if used, should be handled with caution, in order to avoid further depression of ventilation and dependence upon oxygen.

SMALL GASTRIC CANCER.

Comfort, M. W.; Gray, H. K.; Dockerty, M. B., Gage, R. P.; Dornberger, G. R.; Solis, J.; Epperson, D. P., and McNaughton, R. A. *A.M.A. Arch. Int. Med.* **94:** 513 (Oct.) 1954.

The following facts evolved from a study of 226 small gastric adenocarcinomas resected at the Mayo Clinic during the years 1940 to 1945, inclusive: 1) According as the carcinomas were *smaller*, the incidence of high grades of malignancy and of metastasis *declined*, the incidence of ulcer-type symptoms *increased*, symptoms were of *longer* duration, and gastric secretory activity was higher. 2) Also as the carcinomas were smaller, the more they lacked the roentgenologic features of malignancy and the less frequently was their malignant character recognized. 3) Hospital mortality rates were less than those for gastric cancers of all sizes, and approximately equivalent to those for benign gastric ulcer. 4) According as the gastric cancers were smaller, the five-year survival rates were higher. 5) When symptoms were of the ulcer type, or of long duration, or when gastric secretory activity was high, the five-year survival rates were higher than when the reverse of these conditions prevailed. 6) The hope that a small gastric cancer may be more amenable to therapy and entail a better prognosis than gastric cancer in general, is justified by the data obtained in this study. The realization of this hope can be jeopardized by undue prolongation of medical management, and assured by prompt surgical treatment.

RUPTURED ANEURYSMS OF ABDOMINAL AORTA.

Cooley, D. A., and De Bakey, M. E. *Postgrad. Med.* **16:** 334 (Oct.) 1954.

Rupture of aneurysm of the abdominal aorta is the most common and serious complication of such lesions, and it is almost invariably fatal. For uncomplicated aneurysms, resection with replacement by aortic homograft has proved to be an effective method of therapy. It was successfully applied in 2 of 5 cases. The survivors were men aged 50 and 55 years, respectively, who were physically active until the time of rupture of the aneurysm.

The deaths occurred in elderly patients in whom the operation was unavoidably delayed, and who died subsequently of complications of generalized arteriosclerosis. They tolerated the operation well, however, and lived at least three days postoperatively. Rupture of an abdominal aneurysm, this experience shows, may not be immediately fatal and patients appear to survive long enough to provide adequate time to institute surgical treatment. Early diagnosis and aggressive management are mandatory if the operation is to be successful. The technic is described.

TREATMENT OF HYPERTENSION. LONG-TERM RESULTS WITH ALSEROXYLON (RAUWILOID) ALONE AND COMBINED WITH HEXAMETHONIUM ADMINISTERED ORALLY.

Dennis, E.; McConn, R. G.; Ford, R. V.; Hughes, W. M.; Beazley, H. L., and Moyer, J. H. *Postgrad. Med.* **16:** 300 (Oct.) 1954.

1. In a group of 24 patients with hypertension of varying degrees of severity, who were treated with alseroxylon alone for one year or more, the response was just as great after twelve months of continuous treatment as it was after the initial six months of therapy. 2. In a group of 66 patients with varying degrees of hypertension who were treated with combined alseroxylon and hexamethonium therapy for at least one year, 89 per cent maintained a reduction in upright mean blood pressure of 20 mm. Hg or more during the six to twelve months of treatment. About half the patients became normotensive. 3. The blood-pressure reduction during combined alseroxylon and hexamethonium therapy was primarily orthostatic. 4. The blood-pressure reduction during combined alseroxylon and hexamethonium therapy was greater in degree and more stable than with hexamethonium alone, which was used previously under the same conditions of study. The addition of alseroxylon to hexamethonium therapy decreased the incidence and severity of side effects.

BILATERAL ADRENALECTOMY FOR ADVANCED CARCINOMA OF THE BREAST WITH PRELIMINARY OBSERVATIONS ON THE EFFECT OF THE LIVER ON THE METABOLISM OF ADRENAL CORTICAL STEROIDS.

Galante, M.; Rukes, J. M.; Forsham, P. H.; Wood, D. A., and Bell, H. G. *Ann. Surg.* **140:** 502 (Oct.) 1954.

Thirty-one cases of metastatic carcinoma of the breast were treated by bilateral oophorectomy and adrenalectomy. There was no correlation between the histologic picture and the response to the operative procedures. Two cases of adenocarcinoma showed the best results. Objective improvement occurred in 22 per cent of the patients. These changes included marked osteosclerosis of destructive bone lesions, healing of ulcerations of the skin, and regression of soft-tissue masses. Subjective improvement, found in 45 per cent, was most noticeable with regard to bone pain. Large doses of cortisone may have been a factor in postoperative disappearance of pain. However, the pain persisted while the patients were receiving low maintenance dosages of this drug. Patients generally ate better and gained weight while receiving cortisone postoperatively, 37.5 to 50 mg. being required to achieve this result. In some patients objective progression of the disease occurred despite subjective improvement. In the management of these patients, desoxycorticosterone is used only in maintenance therapy. Hydrocortisone intravenously may be substituted for cortisone preparations preoperatively. An experimental procedure was used in 1 case in which, following removal of both ovaries and the right adrenal gland, the blood from the left adrenal gland was shunted through the splenic vein into the portal circulation. Urinary excretion of corticosteroids was unchanged, the excretion of 17-ketosteroids markedly diminished, and estrogens were absent from the urine following this procedure. The patient has done well without substitution therapy. It cannot yet be predicted whether bilateral adrenalectomy combined with oophorectomy will prolong survival time. It offers an additional therapeutic step when patients have not responded to established methods of therapy.

RENAL PAPILLARY NECROSIS: A CLINICOPATHOLOGIC STUDY.

Garrett, R. A.; Norris, M. S., and Vellios, F. *J. Urol.* **72:** 609 (Oct.) 1954.

Papillary necrosis must be suspected in diabetics with severe renal infection or renal failure. The diagnosis can be confirmed by histologic examination of sloughed tissue or pyelographic studies showing ring shadows. Ragged or isolated clubbed calyces are strongly suggestive of this lesion. Nephrectomy in the acute unilateral disease may be beneficial. In bilateral disease, diabetic control, antibacterial therapy and promotion of free urinary drainage are the only courses of action available. Six cases of papillary necrosis are reported, one in detail. (Authors' summary.)

HYPERLIPOPROTEINEMIA.

Gofman, J. W.; Rubin, L.; McGinley, J. P., and Jones, H. B. *Am. J Med.* **17:** 514 (Oct.) 1954.

Serum lipoprotein determinations were made in groups of patients with xanthoma tendinosum, xanthoma tuberosum, xanthelasma, the nephrotic syndrome, biliary cirrhosis, myxedema, and "essential" hyperlipemia. The results are compared with each other and with the normal serum lipoprotein distribution. The serum lipoprotein spectrum can be used for (a) the diagnosis of the nephrotic syndrome and of biliary cirrhosis, (b) the differentiation of xanthoma tuberosum and "essential" hyperlipemia from the other conditions named, and usually from each other, and (c) the differentiation of xanthoma tendinosum, xanthelasma, and myxedema from the other conditions named. The serum lipoprotein spectra in the last three conditions are so similar that they render exceedingly difficult the differential diagnosis by serum lipoprotein levels alone. As the standard diagnostic feature of these illnesses, the serum lipoprotein spectrum would serve better than determination of serum turbidity or cholesterol concentration.

CLINICAL APPLICATION OF CYTOLOGY TO PROSTATIC CANCER.

Gunn, S. A.; Ayre, J. E.; Coplan, M. M.; Woods, F. M., and Melvin, P. D. *J. Urol.* **72:** 722 (Oct.) 1954.

The application of cytology to the detection of early cancer of the prostate is re-evaluated. A method of obtaining cells is outlined. Whenever possible an attempt was made to verify the cytologic diagnosis by specific prostatic serum acid-phosphatase determinations, biopsy, operative material, and necropsy examinations. Among 533 cases thus far studied, 99 examinations were unsatisfactory and 434 were graded cytologically. Among these were 49 graded as suspicious, and 51 as positive for carcinoma. The incidence of suspicious or positive cytologic findings in benign prostatic hypertrophy was 10.7 per cent, in prostatitis, 21.6 per cent, and in a group said to have "no prostatic disease," 19.6 per cent. The survey indicates that benign prostatic hypertrophy is not a precursor of cancer of the prostate and that inflammation plays a causative role no greater than do other factors. Cytologic findings can be used as an index to response to medicinal therapy, as morphologic return to normal is not seen in all treated cases. In untreated clinical cancer of the prostate, cytologic examination corroborated the clinical impression in each case in which there were cells which could be interpreted.

ADRENAL INSUFFICIENCY AS RELATED TO SURGICAL SHOCK.

Hotchkiss, R. S., and Gordon, S. *J. Urol.* **72:** 577 (Oct.) 1954.

Acute adrenal insufficiency is a surgical hazard capable of causing death. It may be precipitated by surgical stress in patients not previously suspected of adrenocortical insufficiency. Normal responses to tests for adrenocortical function do not insure that cortical function is adequate to cope with the stress of an operation. The types of patients who are likely to have a crisis after an operation include: 1) those subjected to an extensive surgical procedure, 2) senile persons with chronic debilitating disease, 3) psychotic pa-

tients, 4) those with urologic disorders, and 5) those who have been treated with cortisone, hydrocortisone, and/or corticotropin. If unexplained shock develops following surgery and is refractory to usual supportive treatment, adrenocortical insufficiency should be suspected and substitution therapy promptly initiated. Four findings may lend support to this diagnosis: 1) marked hypotension, 2) low level of serum sodium, 3) low level of serum chloride, and 4) low carbon-dioxide combining power. When adrenal insufficiency is established prior to operation, treatment should include desoxycorticosterone and cortisone both preoperatively and postoperatively, according to a plan outlined, with glucose in isotonic saline on the day of operation plus parenteral fluids as indicated. When previously unsuspected adrenal insufficiency develops postoperatively, these corticoids also are used (10 mg. of desoxycorticosterone every hour for three doses, and 50 mg. of cortisone every two hours) until the systolic pressure is maintained at 100 mm. Hg. The fluids and electrolytes supplied in this situation include 1,000 cc. of 5 per cent glucose in isotonic saline started at once at a rate of 60–80 drops per minute, followed by a second liter, given more slowly and with 1,000 cc. of 5 per cent glucose in water containing 6 cc. of 1 per cent Neo-Synephrine or 4 mg. of norepinephrine concomitantly through a second vein. The Neo-Synephrine usually can be discontinued four hours after the initiation of salt and hormonal therapy. Subsequent needs for hormones, fluids, and electrolytes are determined by the patient's response.

CHARACTERISTICS OF ADRENAL DEPENDENT MAMMARY CANCERS.

Huggins, C., and Dao, T. L-Y *Ann. Surg.* **140:** 497 (Oct.) 1954.

The postoperative mortality was 5 per cent in a series of 100 women with far-advanced mammary cancer treated by adrenalectomy, with or without oophorectomy. Remissions of varying duration occurred in 38 cases; profound regression of the cancer has persisted for more than thirty-six months. Regression occurred in soft tissue, pleural, peritoneal, hepatic and osseous metastases. The best response occurred in patients: 1) between age 40 and 65, 2) with a prolonged interval between radical mastectomy and onset of metastasis, 3) with a specific histologic type of tumor, 4) with a high titer of estrogenic substances in the urine. Adenocarcinoma of the breast, the most responsive cancer, is composed of spheroids of microscopic dimensions, the malignant acini of which possess a lumen with a lining one cell in thickness. Patients with this cancer excrete considerable quantities of estrogenic substances in the urine and the remaining breast usually secretes milk when tested with luteotropin. Adenocarcinoma stands in a special physiologic category amongst the mammary cancers.

A PHYSIOLOGIC EVALUATION OF THE EFFECTS OF DIAPHRAGMATIC BREATHING TRAINING IN PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA.

Miller, W. F. *Am. J. Med.* **17:** 471 (Oct.) 1954.

Pulmonary function data are presented on 24 patients with chronic pulmonary emphysema who were studied before and after a six- to eight-week period of diaphragmatic breathing training, which was instituted only after a state of optimal improvement had been achieved with long-term, intensive treatment by conventional measures. Increased diaphragmatic excursion, accomplished by this training, resulted in a striking increase in tidal volume at a lower respiratory rate and respiratory mid-position. As a result of these changes, more effective alveolar ventilation was accomplished without significant increase in total ventilation, except in those instances in which it was decreased prior to training. Improved alveolar ventilation was indicated by an increased O_2 removal rate, increased arterial oxygen saturation, decreased arterial pCO_2 and increased exercise tolerance with less dyspnea. This study indicates that diaphragmatic breathing training is an effective adjunct in the treatment of pulmonary emphysema and that such training can be expected in most instances to produce objective improvement in pulmonary function. (Author's summary and conclusions.)

ESOPHAGEAL VARICES IN NONCIRRHOTIC PATIENTS. ESOPHAGOSCOPIC STUDY.

Palmer, E. D., and Brick, I. B. *Am. J. Med.* **17:** 641 (Oct.) 1954.

1). Sixty-two patients with various histologically proven liver diseases other than cirrhosis, and without clinical suspicion of portal vein disease, were studied esophagoscopically. Varices were found in 4 of 7 patients with chronic heart failure, 8 of 14 with active virus hepatitis, 1 of 2 with hemolytic icterus, 1 of 2 with amebic hepatitis and in 8 of 24 with simple portal fibrosis. Varices were not found in 9 instances of fatty liver and in 4 of hepatic sarcoidosis. 2). It is concluded from the observed incidence of varices in these non-cirrhotic diseases that the native portacaval anastomoses across the gastroesophageal junction may quickly respond to an increase in portal pressure by developing into significant varices; that during the course of certain liver diseases, believed to be precirrhotic, varices may already have developed; and that the presence of such varices is not necessarily the explanation for observed hemorrhage. (Authors' summary and conclusions.)

STUDIES IN PASSIVE TRANSFER OF SKIN SENSITIZING ANTIBODIES (ATOPIC REAGINS). THE EFFECTS OF TOPICAL ADMINISTRATION OF STEROIDS ON THE SKIN OF OLD INDIVIDUALS.

Schwartz, M. *Acta allergol.* **7:** 403 (Oct.) 1954.

The size of the wheals induced by passive transfer of a skin sensitizing antibody (hay fever reagin), previously found to be larger in elderly individuals than in younger ones, was not influenced by topical administration of estrogen in women, and testosterone in men. The reason for the larger wheals is obscure.

STUDIES ON THE USE OF ETHAVERINE IN THE TREATMENT OF ANGINA PECTORIS.

Simon, D. L.; Iglauer, A., and Scott, R. C. *Am. Heart J.* **48:** 624 (Oct.) 1954.

Ethaverine, the ethyl analogue of papaverine, in a controlled study of 22 patients with angina pectoris produced no statistically significant reduction in nitroglycerine requirements. It was used at daily dosage levels of 200 and 400 mg. The slight degree of improvement over placebo administration might indicate the need for evaluation of higher dosages in a larger series of patients.

CALCIFICATION OF THE MITRAL VALVE ANNULUS AND ITS RELATION TO FUNCTIONAL VALVULAR DISTURBANCE.

Simon, M. A., and Liu, S. F. *Am. Heart J.* **48:** 497 (Oct.) 1954.

Calcification of the mitral valve annulus is not infrequent. Its incidence was 10 per cent in 590 unselected, consecutive autopsies on subjects of all ages. The incidence was higher in individuals over 50 years of age. Although calcification of the annulus of the mitral valve may occur in rheumatic heart disease, it is primarily a degenerative process, similar in many respects to arteriosclerosis. In the majority of cases the process does not affect the mitral valve leaflets. Variable degrees of calcification of the aortic valve, presumably on a nonrheumatic basis, were associated in approximately 25 per cent of the subjects whose hearts showed calcification of the mitral valve annulus. In a selected series of 24 cases of mitral annulus calcification, apical systolic murmurs, presumably referable to the mitral valve, were heard in 15 cases (62.5 per cent). In 9 of these 15 cases (60.0 per cent) the quality of the murmurs was such (loud, rough or musical) as may be associated with functional derangement at the mitral orifice, and in 5 instances (33.3 per cent) a clinical diagnosis of mitral regurgitation was made. In the light of newer knowledge of the mechanics of the closure of the mitral valve, it is suggested that extensive calcification of the mitral valve annulus interferes with the rhythmic muscular contraction of the mitral ring by forming a rigid, noncompressible segment of that ring. Thus, the gap to be bridged may not be sufficiently reduced to permit the overlapping closure by the mitral leaflets.

This concept of interference with contraction of the valve ring, together with the observation that 60 per cent of apical systolic murmurs in our proved cases of mitral annulus calcification have special qualities suggesting mitral dysfunction, is construed as presumptive evidence that extensive mitral annulus calcification (without rheumatic involvement of the leaflets) may produce relative or frank mitral regurgitation. Whether such mitral regurgitation, either relative or frank, as may be produced by mitral annulus calcification is sufficient to impair further the cardiac function of subjects in an older age group, the majority of whose hearts are already partially damaged, is extremely difficult to assess. Extensive calcification of the mitral valve annulus which may produce variable degrees of mitral regurgitation can be strongly suspected in individuals over 50 years of age having loud, rough or musical systolic apical murmurs, with no history of previous rheumatic heart disease. (Authors' summary and conclusions.)

ZUR BEDEUTUNG DER BLUTUNG IN DER MENOPAUSE (THE SIGNIFICANCE OF BLEEDING IN THE MENOPAUSE).

Stoll, P., and Bach, H. G. *Deutsche med. Wchnschr.* **79:** 1559 (Oct. 15) 1954.

Among 574 women with menopausal bleeding, treated during the years 1951 through 1953, bleeding was due to malignancy in 258 (44.9 per cent). In 316 (55.1 per cent), the cause was a mild genital disorder. Bleeding from a malignant source occurred most frequently between the ages of 55 and 59 years. Bleeding from a nonmalignant source occurred frequently in the 50–54 year age group. In a study of the duration of the menopause up until the first appearance of bleeding, it was found that the longer the time since the cessation of menses, the greater the danger that bleeding was caused by a neoplasm. Among the nonmalignant causes of bleeding were polyps, atrophic endometrium, glandular hyperplasia, endometriosis, erosion, colpitis, myoma, urethral polyps, and ovarian tumor. Biopsy with histologic examination of tissues is recommended as the most certain way to exclude the possibility of a malignancy.

PHRENIC NERVE INTERRUPTION FOR MASSIVE BLEEDING AND OTHER SYMPTOMS OF HIATAL HERNIA.

Walstad, P. M.; and Carlson, E. *Am. J. Surg.* **88:** 535 (Oct.) 1954.

Esophageal hiatal hernia can produce numerous clinical symptoms that mimic those of widely divergent diseases. It may also occur along with the diseases it mimics. It can cause such grave complications as massive hemorrhage, protracted vomiting, and sharp precordial pain. Most hiatal hernias are seen in patients beyond middle age, because laxity of the hiatal supporting structures progresses with advancing age. When complications arise in these patients, they present more difficulty than in patients in younger age groups. Nine cases of hiatal hernia complications in patients aged 47 to 82 years are presented, to show the value of phrenic nerve interruption. The indication for this procedure was severe hematemesis in 4 patients, anemia in 1, and intense pain in 4. In each instance the presence of a hiatal hernia was demonstrated by gastrointestinal series. Under local anesthesia, the left phrenic nerve was interrupted by crushing in 7 patients and by division in 2. From experience in these cases and reference to authoritative opinions on the benefits of the procedure, it is concluded that phrenic nerve interruption is indicated in cases of hiatal hernia with massive hematemesis, to control the hemorrhage until such time as definitive surgery can be performed. It is also indicated in patients with marked upper abdominal and precordial pains, to relieve the pain and to decrease the stress reflexly imposed upon either a normal or diseased heart. It is valuable in clarifying the differentiation between hiatal hernia and heart disease. In elderly individuals in whom a major surgical attack upon hiatal hernia is precluded, but who suffer from pain, bleeding or vomiting, the procedure produces dramatic relief with minimal risk. Phrenic nerve interruption allows the surgeon a precious interlude in the further management of the complications of esophageal hiatal hernia. The complications of bleeding, pain and obstruction in hiatal hernia as regards differential diagnosis and mechanics are discussed.